

WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: C12N 15/12, C07K 14/47, 16/18, C12Q 1/68

(11) International Publication Number:

WO 99/31236

(43) International Publication Date:

24 June 1999 (24.06.99)

(21) International Application Number:

PCT/IB98/02122

A2

(22) International Filing Date:

17 December 1998 (17.12.98)

(30) Priority Data:

60/069,957 17 December 1997 (17.12.97) US 60/074,121 9 February 1998 (09.02.98) US 60/081,563 13 April 1998 (13.04.98) US 10 August 1998 (10.08.98) 60/096,116

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: EXTENDED cDNAs FOR SECRETED PROTEINS

(57) Abstract

The sequences of extended cDNAs encoding secreted proteins are disclosed. The extended cDNAs can be used to express secreted proteins or portions thereof or to obtain antibodies capable of specifically binding to the secreted proteins. The extended cDNAs may also be used in diagnostic, forensic, gene therapy, and chromosome mapping procedures. The extended cDNAs may also be used to design expression vectors and secretion vectors.

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EXTENDED cDNAS for secreted proteins

The present application relates to extended cDNAs which were disclosed in several United States Provisional Patent Applications. Table I lists the SEQ ID Nos. of the extended cDNAs in the present application, the SEQ ID Nos. of the identical or nearly identical extended cDNAs in the provisional applications, and the identities of the provisional applications in which the extended cDNAs were disclosed.

Background of the Invention

The estimated 50,000-100,000 genes scattered along the human chromosomes offer tremendous promise for the understanding, diagnosis, and treatment of human diseases. In addition, probes capable of specifically hybridizing to loci distributed throughout the human genome find applications in the construction of high resolution chromosome maps and in the identification of individuals.

In the past, the characterization of even a single human gene was a painstaking process, requiring years of effort. Recent developments in the areas of cloning vectors, DNA sequencing, and computer technology have merged to greatly accelerate the rate at which human genes can be isolated, sequenced, mapped, and characterized. Cloning vectors such as yeast artificial chromosomes (YACs) and bacterial artificial chromosomes (BACs) are able to accept DNA inserts ranging from 300 to 1000 kilobases (kb) or 100-400 kb in length respectively, thereby facilitating the manipulation and ordering of DNA sequences distributed over great distances on the human chromosomes. Automated DNA sequencing machines permit the rapid sequencing of human genes. Bioinformatics software enables the comparison of nucleic acid and protein sequences, thereby assisting in the characterization of human gene products.

Currently, two different approaches are being pursued for identifying and characterizing the genes distributed
along the human genome. In one approach, large fragments of genomic DNA are isolated, cloned, and sequenced.
Potential open reading frames in these genomic sequences are identified using bio-informatics software. However, this approach entails sequencing large stretches of human DNA which do not encode proteins in order to find the protein encoding sequences scattered throughout the genome. In addition to requiring extensive sequencing, the bio-informatics software may mischaracterize the genomic sequences obtained. Thus, the software may produce-false positives in which non-coding DNA is mischaracterized as coding DNA or false negatives in which coding DNA is mislabeled as non-coding DNA.

An alternative approach takes a more direct route to identifying and characterizing human genes. In this approach, complementary DNAs (cDNAs) are synthesized from isolated messenger RNAs (mRNAs) which encode human proteins. Using this approach, sequencing is only performed on DNA which is derived from protein coding portions of the genome. Often, only short stretches of the cDNAs are sequenced to obtain sequences called expressed sequence tags (ESTs). The ESTs may then be used to isolate or purify extended cDNAs which include sequences adjacent to the EST sequences. The extended cDNAs may contain all of the sequence of the EST which was used to obtain them or only a portion of the sequence of the EST which was used to obtain them. In addition, the extended cDNAs may contain the full coding sequence of the gene from which the EST was derived or, alternatively, the extended cDNAs may include

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portions of the coding sequence of the gene from which the EST was derived. It will be appreciated that there may be several extended cDNAs which include the EST sequence as a result of alternate splicing or the activity of alternative promoters.

In the past, the short EST sequences which could be used to isolate or purify extended cDNAs were often 5 obtained from oligo-dT primed cDNA libraries. Accordingly, they mainly corresponded to the 3' untranslated region of the mRNA. In part, the prevalence of EST sequences derived from the 3' end of the mRNA is a result of the fact that typical techniques for obtaining cDNAs, are not well suited for isolating cDNA sequences derived from the 5' ends of mRNAs. (Adams et al., Nature 377:174, 1996, Hillier et al., Genome Res. 6:807-828, 1996).

In addition, in those reported instances where longer cDNA sequences have been obtained, the reported 10 sequences typically correspond to coding sequences and do not include the full 5' untranslated region of the mRNA from which the cDNA is derived. Such incomplete sequences may not include the first exon of the mRNA, particularly in situations where the first exon is short. Furthermore, they may not include some exons, often short ones, which are located upstream of splicing sites. Thus, there is a need to obtain sequences derived from the 5' ends of mRNAs which can be used to obtain extended cDNAs which may include the 5' sequences contained in the 5' ESTs.

While many sequences derived from human chromosomes have practical applications, approaches based on the identification and characterization of those chromosomal sequences which encode a protein product are particularly relevant to diagnostic and therapeutic uses. Of the 50,000-100,000 protein coding genes, those genes encoding proteins which are secreted from the cell in which they are synthesized, as well as the secreted proteins themselves, are particularly valuable as potential therapeutic agents. Such proteins are often involved in cell to cell communication and 20 may be responsible for producing a clinically relevant response in their target cells.

In fact, several secretory proteins, including tissue plasminogen activator, G-CSF, GM-CSF, erythropoietin, human growth hormone, insulin, interferon-α, interferon-β, interferon-γ, and interleukin-2, are currently in clinical use. These proteins are used to treat a wide range of conditions, including acute myocardial infarction, acute ischemic stroke, anemia, diabetes, growth hormone deficiency, hepatitis, kidney carcinoma, chemotherapy induced neutropenia and 25 multiple sclerosis. For these reasons, extended cDNAs encoding secreted proteins or portions thereof represent a particularly valuable source of therapeutic agents. Thus, there is a need for the identification and characterization of secreted proteins and the nucleic acids encoding them.

In addition to being therapeutically useful themselves, secretory proteins include short peptides, called signal peptides, at their amino termini which direct their secretion. These signal peptides are encoded by the signal sequences 30 located at the 5' ends of the coding sequences of genes encoding secreted proteins. Because these signal peptides will direct the extracellular secretion of any protein to which they are operably linked, the signal sequences may be exploited to direct the efficient secretion of any protein by operably linking the signal sequences to a gene encoding the protein for which secretion is desired. This may prove beneficial in gene therapy strategies in which it is desired to deliver a particular gene product to cells other than the cell in which it is produced. Signal sequences encoding signal peptides

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also find application in simplifying protein purification techniques. In such applications, the extracellular secretion of the desired protein greatly facilitates purification by reducing the number of undesired proteins from which the desired protein must be selected. Thus, there exists a need to identify and characterize the 5' portions of the genes for secretory proteins which encode signal peptides.

Public information on the number of human genes for which the promoters and upstream regulatory regions have been identified and characterized is quite limited. In part, this may be due to the difficulty of isolating such regulatory sequences. Upstream regulatory sequences such as transcription factor binding sites are typically too short to be utilized as probes for isolating promoters from human genomic libraries. Recently, some approaches have been developed to isolate human promoters. One of them consists of making a CpG island library (Cross, S.H. et al., 10 Purification of CpG Islands using a Methylated DNA Binding Column, Nature Genetics 6: 236-244 (1994)). The second consists of isolating human genomic DNA sequences containing Spel binding sites by the use of Spel binding protein. (Mortlock et al., Genome Res. 6:327-335, 1996). Both of these approaches have their limits due to a lack of specificity or of comprehensiveness.

5' ESTs and extended cDNAs obtainable therefrom may be used to efficiently identify and isolate upstream 15 regulatory regions which control the location, developmental stage, rate, and quantity of protein synthesis, as well as the stability of the mRNA. (Theil et al., BioFactors 4:87-93, (1993). Once identified and characterized, these regulatory regions may be utilized in gene therapy or protein purification schemes to obtain the desired amount and locations of protein synthesis or to inhibit, reduce, or prevent the synthesis of undesirable gene products.

In addition, ESTs containing the 5' ends of secretory protein genes or extended cDNAs which include 20 sequences adjacent to the sequences of the ESTs may include sequences useful as probes for chromosome mapping and the identification of individuals. Thus, there is a need to identify and characterize the sequences upstream of the 5' coding sequences of genes encoding secretory proteins.

Summary of the Invention

The present invention relates to purified, isolated, or recombinant extended cDNAs which encode secreted 25 proteins or fragments thereof. Preferably, the purified, isolated or recombinant cDNAs contain the entire open reading frame of their corresponding mRNAs, including a start codon and a stop codon. For example, the extended cDNAs may include nucleic acids encoding the signal peptide as well as the mature protein. Alternatively, the extended cDNAs may contain a fragment of the open reading frame. In some embodiments, the fragment may encode only the sequence of the mature protein. Alternatively, the fragment may encode only a portion of the mature protein. A further aspect of the present invention is a nucleic acid which encodes the signal peptide of a secreted protein.

The present extended cDNAs were obtained using ESTs which include sequences derived from the authentic 5' ends of their corresponding mRNAs. As used herein the terms "EST" or "5' EST" refer to the short cDNAs which were used to obtain the extended cDNAs of the present invention. As used herein, the term "extended cDNA" refers to the cDNAs which include sequences adjacent to the 5' EST used to obtain them. The extended cDNAs may contain all or a

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portion of the sequence of the EST which was used to obtain them. The term "corresponding mRNA" refers to the mRNA which was the template for the cDNA synthesis which produced the 5' EST. As used herein, the term "purified" does not require absolute purity; rather, it is intended as a relative definition. Individual extended cDNA clones isolated from a cDNA library have been conventionally purified to electrophoretic homogeneity. The sequences obtained from these clones could not be obtained directly either from the library or from total human DNA. The extended cDNA clones are not naturally occurring as such, but rather are obtained via manipulation of a partially purified naturally occurring substance (messenger RNA). The conversion of mRNA into a cDNA library involves the creation of a synthetic substance (cDNA) and pure individual cDNA clones can be isolated from the synthetic library by clonal selection. Thus, creating a cDNA library from messenger RNA and subsequently isolating individual clones from that library results in an approximately 10⁴·10⁶ fold purification of the native message. Purification of starting material or natural material to at least one order of magnitude, preferably two or three orders, and more preferably four or five orders of magnitude is expressly contemplated.

As used herein, the term "isolated" requires that the material be removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide present in a living animal is not isolated, but the same polynucleotide, separated from some or all of the coexisting materials in the natural system, is isolated.

As used herein, the term "recombinant" means that the extended cDNA is adjacent to "backbone" nucleic acid to which it is not adjacent in its natural environment. Additionally, to be "enriched" the extended cDNAs will represent 5% or more of the number of nucleic acid inserts in a population of nucleic acid backbone molecules. Backbone molecules according to the present invention include nucleic acids such as expression vectors, self-replicating nucleic acids, viruses, integrating nucleic acids, and other vectors or nucleic acids used to maintain or manipulate a nucleic acid insert of interest. Preferably, the enriched extended cDNAs represent 15% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. More preferably, the enriched extended cDNAs represent 50% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. In a highly preferred embodiment, the enriched extended cDNAs represent 90% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. "Stringent", "moderate," and "low" hybridization conditions are as defined in Example 29.

Unless otherwise indicated, a "complementary" sequence is fully complementary. Thus, extended cDNAs encoding secreted polypeptides or fragments thereof which are present in cDNA libraries in which one or more extended cDNAs encoding secreted polypeptides or fragments thereof make up 5% or more of the number of nucleic acid inserts in the backbone molecules are "enriched recombinant extended cDNAs" as defined herein. Likewise, extended cDNAs encoding secreted polypeptides or fragments thereof which are in a population of plasmids in which one or more extended cDNAs of the present invention have been inserted such that they represent 5% or more of the number of inserts in the plasmid backbone are "enriched recombinant extended cDNAs" as defined herein. However, extended

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cDNAs encoding secreted polypeptides or fragments thereof which are in cDNA libraries in which the extended cDNAs encoding secreted polypeptides or fragments thereof constitute less than 5% of the number of nucleic acid inserts in the population of backbone molecules, such as libraries in which backbone molecules having a cDNA insert encoding a secreted polypeptide are extremely rare, are not "enriched recombinant extended cDNAs."

In particular, the present invention relates to extended cDNAs which were derived from genes encoding secreted proteins. As used herein, a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal peptides in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g. soluble proteins), or partially (e.g. receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are 10 transported across the membrane of the endoplasmic reticulum.

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Extended cDNAs encoding secreted proteins may include nucleic acid sequences, called signal sequences. which encode signal puptides which direct the extracellular secretion of the proteins encoded by the extended cDNAs. Generally, the signal peptides are located at the amino termini of secreted proteins.

Secreted proteins are translated by ribosomes associated with the "rough" endoplasmic reticulum. Generally, 15 secreted proteins are co-translationally transferred to the membrane of the endoplasmic reticulum. Association of the ribosome with the endoplasmic reticulum during translation of secreted proteins is mediated by the signal peptide. The signal peptide is typically cleaved following its co-translational entry into the endoplasmic reticulum. After delivery to the endoplasmic reticulum, secreted proteins may proceed through the Golgi apparatus. In the Golgi apparatus, the proteins may undergo post-translational modification before entering secretory vesicles which transport them across the 20 cell membrane.

The extended cDNAs of the present invention have several important applications. For example, they may be used to express the entire secreted protein which they encode. Alternatively, they may be used to express portions of the secreted protein. The portions may comprise the signal peptides encoded by the extended cDNAs or the mature proteins encoded by the extended cDNAs (i.e. the proteins generated when the signal peptide is cleaved off). The 25 portions may also comprise polypeptides having at least 10 consecutive amino acids encoded by the extended cDNAs. Alternatively, the portions may comprise at least 15 consecutive amino acids encoded by the extended cDNAs. In some embodiments, the portions may comprise at least 25 consecutive amino acids encoded by the extended cDNAs. In other embodiments, the portions may comprise at least 40 amino acids encoded by the extended cDNAs.

Antibodies which specifically recognize the entire secreted proteins encoded by the extended cDNAs or 30 fragments thereof having at least 10 consecutive amino acids, at least 15 consecutive amino acids, at least 25 consecutive amino acids, or at least 40 consecutive amino acids may also be obtained as described below. Antibodies which specifically recognize the mature protein generated when the signal peptide is cleaved may also be obtained as described below. Similarly, antibodies which specifically recognize the signal peptides encoded by the extended cDNAs may also be obtained.

In some embodiments, the extended cDNAs include the signal sequence. In other embodiments, the extended cDNAs may include the full coding sequence for the mature protein (i.e. the protein generated when the signal polypeptide is cleaved off). In addition, the extended cDNAs may include regulatory regions upstream of the translation start site or downstream of the stop codon which control the amount, location, or developmental stage of gene expression. As discussed above, secreted proteins are therapeutically important. Thus, the proteins expressed from the cDNAs may be useful in treating or controlling a variety of human conditions. The extended cDNAs may also be used to obtain the corresponding genomic DNA. The term "corresponding genomic DNA" refers to the genomic DNA which encodes mRNA which includes the sequence of one of the strands of the extended cDNA in which thymidine residues in the sequence of the extended cDNA are replaced by uracil residues in the mRNA.

The extended cDNAs or genomic DNAs obtained therefrom may be used in forensic procedures to identify individuals or in diagnostic procedures to identify individuals having genetic diseases resulting from abnormal expression of the genes corresponding to the extended cDNAs. In addition, the present invention is useful for constructing a high resolution map of the human chromosomes.

The present invention also relates to secretion vectors capable of directing the secretion of a protein of
interest. Such vectors may be used in gene therapy strategies in which it is desired to produce a gene product in one cell
which is to be delivered to another location in the body. Secretion vectors may also facilitate the purification of desired
proteins.

The present invention also relates to expression vectors capable of directing the expression of an inserted gene in a desired spatial or temporal manner or at a desired level. Such vectors may include sequences upstream of the extended cDNAs such as promoters or upstream regulatory sequences.

In addition, the present invention may also be used for gene therapy to control or treat genetic diseases. Signal peptides may also be fused to heterologous proteins to direct their extracellular secretion.

One embodiment of the present invention is a purified or isolated nucleic acid comprising the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary thereto. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid comprising at least 10 consecutive bases of the sequence of one of SEQ ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto. In one aspect of this embodiment, the nucleic acid comprises at least 15, 25, 30, 40, 50, 75, or 100 consecutive bases of one of the sequences of SEQ ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto. The nucleic acid may be a recombinant nucleic acid.

Another embodiment of the present invention is a purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent conditions to the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary to one of the sequences of SEQ ID NOs: 40-140 and 242-377. In one aspect of this embodiment, the nucleic acid is recombinant.

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Another embodiment of the present invention is a purified or isolated nucleic acid comprising the full coding sequences of one of SEQ ID NOs: 40-140 and 242-377, wherein the full coding sequence optionally comprises the sequence encoding signal peptide as well as the sequence encoding mature protein. In a preferred embodiment, the isolated or purified nucleic acid comprises the full coding sequence of one of SEQ ID Nos. 40, 42-44, 46, 48, 49, 51, 53, 60, 62-72, 76-78, 80-83, 85-88, 90, 93, 94, 97, 99-102, 104, 107-125, 127, 132, 135-138, 140 and 242-377 wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein. In one aspect of this embodiment, the nucleic acid is recombinant.

A further embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-140 and 242-377 which encode a mature protein. In a preferred embodiment, the purified or isolated nucleic acid comprises the nucleotides of one of SEQ ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein. In one aspect of this embodiment, the nucleic acid is recombinant.

Yet another embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEO ID NOs: 40-140 and 242-377 which encode the signal peptide. In a preferred embodiment, the purified or isolated nucleic acid comprises the nucleotides of SEO ID NOs: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140 and 242-377 which encode the signal peptide. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a signal peptide included in one of the sequences of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.

Yet another embodiment of the present invention is a purified or isolated protein comprising the sequence of one of SEO ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is a purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In one aspect of this embodiment, the purified or isolated polypeptide comprises at least 15, 20, 25, 35, 50, 75, 100, 150 or 200 consecutive

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amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In still another aspect, the purified or isolated polypeptide comprises at least 25 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is an isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the isolated or purified polypeptide comprises a signal peptide of one of the polypeptides of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.

Yet another embodiment of the present invention is an isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the isolated or purified polypeptide comprises a mature protein of one of the polypeptides of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.

A further embodiment of the present invention is a method of making a protein comprising one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the sequences of sequence of SEQ ID NO: 40-140 and 242-377, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the protein encoded by said cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a protein obtainable by the method described in the preceding paragraph.

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Another embodiment of the present invention is a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the nucleotides sequence of sequence of SEQ ID NO: 40-140 and 242-377 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a mature protein obtainable by the method described in the preceding paragraph.

In a preferred embodiment, the above method comprises a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NO: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the nucleotides sequence of sequence of SEQ ID NO:

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40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of 5 isolating the protein.

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Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary thereto described herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids 10 comprising the full coding sequences of one of SEQ ID NOs: 40-140 and 242-377, wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein described herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 40-140 and 242-377 which encode a mature protein which are described herein. Preferably, the host cell contains the purified or isolated nucleic acids comprising the nucleotides of 15 one of SEQ ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEQ ID NOs: 40-140 and 242-377 which encode the signal peptide which are described herein. Preferably, the host cell contains the purified or isolated nucleic acids comprising the nucleotides of 20 one of SEQ ID Nos.: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140 and 242-377 which encode the signal peptide.

Another embodiment of the present invention is a purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEQ ID NOs: 141-241 and 378-513. In one aspect of this embodiment, the antibody is capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of 25 SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is an array of cDNAs or fragments thereof of at least 15 nucleotides in length which includes at least one of the sequences of SEQ ID NOs: 40-140 and 242-377, or one of the sequences complementary to the sequences of SEO ID NOs: 40-140 and 242-377, or a fragment thereof of at least 15 consecutive nucleotides. In one aspect of this embodiment, the array includes at least two of the sequences of SEQ ID 30 NOs: 40-140 and 242-377, the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or fragments thereof of at least 15 consecutive nucleotides. In another aspect of this embodiment, the array includes at least five of the sequences of SEQ ID NOs: 40-140 and 242-377, the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or fragments thereof of at least 15 consecutive nucleotides.

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A further embodiment of the invention encompasses purified polynucleotides comprising an insert from a clone deposited in a deposit having an accession number selected from the group consisting of the accession numbers listed in Table VI or a fragment thereof comprising a contiguous span of at least 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 nucleotides of said insert. An additional embodiment of the invention encompasses purified polypeptides which comprise, consist of, or consist essentially of an amino acid sequence encoded by the insert from a clone deposited in a deposit having an accession number selected from the group consisting of the accession numbers listed in Table VI, as well as polypeptides which comprise a fragment of said amino acid sequence consisting of a signal peptide, a mature protein, or a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 amino acids encoded by said insert.

An additional embodiment of the invention encompasses purified polypeptides which comprise a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 amino acids of SEQ ID NOs: 158, 174, 175, 196, 226, 231, 232, wherein said contiguous span comprises at least one of the amino acid positions which was not shown to be identical to a public sequence in any of Figures 11 to 15. Also encompassed by the invention are purified polynuculeotides encoding said polypeptides.

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Brief Description of the Drawings

Figure 1 is a summary of a procedure for obtaining cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived.

Figure 2 is an analysis of the 43 amino terminal amino acids of all human SwissProt proteins to determine the frequency of false positives and false negatives using the techniques for signal peptide identification described herein.

Figure 3 shows the distribution of von Heijne scores for 5' ESTs in each of the categories described herein and the probability that these 5' ESTs encode a signal peptide.

Figure 4 shows the distribution of 5' ESTs in each category and the number of 5' ESTs in each category having a given minimum von Heijne's score.

Figure 5 shows the tissues from which the mRNAs corresponding to the 5' ESTs in each of the categories described herein were obtained.

Figure 6 illustrates a method for obtaining extended cDNAs.

Figure 7 is a map of pED6dpc2. pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SSt cDNAs are cloned between EcoRI and Not1. PED vectors are described in Kaufman et al. 30 (1991), NAR 19: 4485-4490.

Figure 8 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5' tags.

Figure 9 describes the transcription factor binding sites present in each of these promoters.

Figure 10 is an alignment of the protein of SEQ ID NO: 217 with the human protein TFAR19 that may play a role in apoptosis (Genbank accession number AF014955, SEQ ID NO: 516).

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Figure 11 is an alignment of the proteins of SEQ ID NOs: 174, 175 and 232 with a human secreted protein (Genseg accession number W36955, SEQ ID NO: 517).

Figure 12 is an alignment of the protein of SEQ ID NO: 231 with the human E25 protein (Genbank accession number AF038953, SEQ ID NO: 515).

Figure 13 is an alignment of the protein of SEQ ID NO: 196 with the human seventransmembrane protein (Genbank accession number Y11395, SEQ ID NO: 518).

Figure 14 is an alignment of the protein of SEQ ID NOs: 158 with the murine subunit 7a of the COP9 complex 10 (Genbank accession number AF071316, SEQ ID NO: 519).

Figure 15 is an alignment of the protein of SEQ ID NO: 226 with the bovine subunit B14.5B of the NADHubiquinone oxidureductase complex (Arizmendi *et al, FEBS Lett.*, **313** : 80-84 (1992) and Swissprot accession -number Q02827, SEQ ID NO: 514).

Detailed Description of the Preferred Embodiment

15 1. Obtaining 5' ESTs

The present extended cDNAs were obtained using 5' ESTs which were isolated as described below.

A. Chemical Methods for Obtaining mRNAs having Intact 5' Ends

In order to obtain the 5' ESTs used to obtain the extended cDNAs of the present invention, mRNAs having intact 5' ends must be obtained. Currently, there are two approaches for obtaining such mRNAs. One of these 20 approaches is a chemical modification method involving derivatization of the 5' ends of the mRNAs and selection of the derivatized mRNAs. The 5' ends of eucaryotic mRNAs possess a structure referred to as a "cap" which comprises a guanosine methylated at the 7 position. The cap is joined to the first transcribed base of the mRNA by a 5', 5'triphosphate bond. In some instances, the 5' guanosine is methylated in both the 2 and 7 positions. Rarely, the 5' guanosine is trimethylated at the 2, 7 and 7 positions. In the chemical method for obtaining mRNAs having intact 5' 25 ends, the 5' cap is specifically derivatized and coupled to a reactive group on an immobilizing substrate. This specific derivatization is based on the fact that only the ribose linked to the methylated guanosine at the 5' end of the mRNA and the ribose linked to the base at the 3' terminus of the mRNA, possess 2', 3'-cis diols. Optionally, where the 3' terminal ribose has a 2', 3'-cis diol, the 2', 3'-cis diol at the 3' end may be chemically modified, substituted, converted, or eliminated, leaving only the ribose linked to the methylated guanosine at the 5' end of the mRNA with a 2', 3'-cis diol. A 30 variety of techniques are available for eliminating the 2', 3'-cis diol on the 3' terminal ribose. For example, controlled alkaline hydrolysis may be used to generate mRNA fragments in which the 3' terminal ribose is a 3'-phosphate, 2'phosphate or (2', 3')-cyclophosphate. Thereafter, the fragment which includes the original 3' ribose may be eliminated from the mixture through chromatography on an oligo-dT column. Alternatively, a base which lacks the 2', 3'-cis diol

may be added to the 3' end of the mRNA using an RNA ligase such as T4 RNA ligase. Example 1 below describes a method for ligation of pCp to the 3' end of messenger RNA.

EXAMPLE 1

Ligation of the Nucleoside Diphosphate pCp to the 3' End of Messenger RNA

1 μ g of RNA was incubated in a final reaction medium of 10 μ l in the presence of 5 U of T₄ phage RNA ligase in the buffer provided by the manufacturer (Gibco - BRL), 40 U of the RNase inhibitor RNasin (Promega) and, 2 μ l of ³²pCp (Amersham #PB 10208).

The incubation was performed at 37°C for 2 hours or overnight at 7-8°C.

Following modification or elimination of the 2', 3'-cis diol at the 3' ribose, the 2', 3'-cis diol present at the 5' end of the mRNA may be oxidized using reagents such as NaBH₄, NaBH₃CN, or sodium periodate, thereby converting the 2', 3'-cis diol to a dialdehyde. Example 2 describes the oxidation of the 2', 3'-cis diol at the 5' end of the mRNA with sodium periodate.

EXAMPLE 2

Oxidation of 2', 3'-cis diol at the 5' End of the mRNA

O.1 OD unit of either a capped oligoribonucleotide of 47 nucleotides (including the cap) or an uncapped oligoribonucleotide of 46 nucleotides were treated as follows. The oligoribonucleotides were produced by in vitro transcription using the transcription kit "AmpliScribe T7" (Epicentre Technologies). As indicated below, the DNA template for the RNA transcript contained a single cytosine. To synthesize the uncapped RNA, all four NTPs were included in the in vitro transcription reaction. To obtain the capped RNA, GTP was replaced by an analogue of the cap, m7G(5')ppp(5')G. This compound, recognized by polymerase, was incorporated into the 5' end of the nascent transcript during the step of initiation of transcription but was not capable of incorporation during the extension step.

Consequently, the resulting RNA contained a cap at its 5' end. The sequences of the oligoribonucleotides produced by the in vitro transcription reaction were:

+Cap:

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25 5'm7GpppGCAUCCUACUCCCAUCCAAUUCCACCCUAACUCCUCCCAUCUCCAC-3' (SEQ ID NO:1)

-Cap:

5'-pppGCAUCCUACUCCCAUCCAAUUCCACCCUAACUCCUCCCAUCUCCAC-3' (SEQ ID NO:2)

The oligoribonucleotides were dissolved in 9 µl of acetate buffer (0.1 M sodium acetate, pH 5.2) and 3 µl of freshly prepared 0.1 M sodium periodate solution. The mixture was incubated for 1 hour in the dark at 4°C or room temperature. Thereafter, the reaction was stopped by adding 4 µl of 10% ethylene glycol. The product was ethanol precipitated, resuspended in 10µl or more of water or appropriate buffer and dialyzed against water.

The resulting aldehyde groups may then be coupled to molecules having a reactive amine group, such as hydrazine, carbazide, thiocarbazide or semicarbazide groups, in order to facilitate enrichment of the 5' ends of the mRNAs. Molecules having reactive amine groups which are suitable for use in selecting mRNAs having intact 5' ends

include avidin, proteins, antibodies, vitamins, ligands capable of specifically binding to receptor molecules, or oligonucleotides. Example 3 below describes the coupling of the resulting dialdehyde to biotin.

EXAMPLE 3

Coupling of the Dialdehyde with Biotin

The oxidation product obtained in Example 2 was dissolved in 50 µl of sodium acetate at a pH of between 5 and 5.2 and 50 µl of freshly prepared 0.02 M solution of biotin hydrazide in a methoxyethanol/water mixture (1:1) of formula:

In the compound used in these experiments, n=5. However, it will be appreciated that other commercially available hydrazides may also be used, such as molecules of the formula above in which n varies from 0 to 5.

The mixture was then incubated for 2 hours at 37°C. Following the incubation, the mixture was precipitated with ethanol and dialyzed against distilled water.

Example 4 demonstrates the specificity of the biotinylation reaction.

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EXAMPLE 4

Specificity of Biotinylation

The specificity of the biotinylation for capped mRNAs was evaluated by gel electrophoresis of the following samples:

- Sample 1. The 46 nucleotide uncapped in vitro transcript prepared as in Example 2 and labeled with ³²pCp as described in Example 1.
 - Sample 2. The 46 nucleotide uncapped in vitro transcript prepared as in Example 2, labeled with ³²pCp as described in Example 1, treated with the oxidation reaction of Example 2, and subjected to the biotinylation conditions of Example 3.
- Sample 3. The 47 nucleotide capped in vitro transcript prepared as in Example 2 and labeled with ³²pCp as described in Example 1.
 - Sample 4. The 47 nucleotide capped in vitro transcript prepared as in Example 2, labeled with ³²pCp as described in Example 1, treated with the oxidation reaction of Example 2, and subjected to the biotinylation conditions of Example 3.

Samples 1 and 2 had indentical migration rates, demonstrating that the uncapped RNAs were not oxidized and 30 biotinylated. Sample 3 migrated more slowly than Samples 1 and 2, while Sample 4 exhibited the slowest migration.

The difference in migration of the RNAs in Samples 3 and 4 demonstrates that the capped RNAs were specifically biotinylated.

In some cases, mRNAs having intact 5' ends may be enriched by binding the molecule containing a reactive amine group to a suitable solid phase substrate such as the inside of the vessel containing the mRNAs, magnetic beads, chromatography matrices, or nylon or nitrocellulose membranes. For example, where the molecule having a reactive amine group is biotin, the solid phase substrate may be coupled to avidin or streptavidin. Alternatively, where the molecule having the reactive amine group is an antibody or receptor ligand, the solid phase substrate may be coupled to the cognate antigen or receptor. Finally, where the molecule having a reactive amine group comprises an oligonucleotide, the solid phase substrate may comprise a complementary oligonucleotide.

The mRNAs having intact 5' ends may be released from the solid phase following the enrichment procedure.

For example, where the dialdehyde is coupled to biotin hydrazide and the solid phase comprises streptavidin, the mRNAs may be released from the solid phase by simply heating to 95 degrees Celsius in 2% SDS. In some methods, the molecule having a reactive amine group may also be cleaved from the mRNAs having intact 5' ends following enrichment.

Example 5 describes the capture of biotinylated mRNAs with streptavidin coated beads and the release of the biotinylated mRNAs from the beads following enrichment.

EXAMPLE 5

Capture and Release of Biotinylated mRNAs Using Strepatividin Coated Beads

The streptavidin-coated magnetic beads were prepared according to the manufacturer's instructions (CPG Inc., USA). The biotinylated mRNAs were added to a hybridization buffer (1.5 M NaCl, pH 5 - 6). After incubating for 30 minutes, the unbound and nonbiotinylated material was removed. The beads were washed several times in water with 1% SDS. The beads obtained were incubated for 15 minutes at 95°C in water containing 2% SDS.

Example 6 demonstrates the efficiency with which biotinylated mRNAs were recovered from the streptavidin coated beads.

EXAMPLE 6

25 <u>Efficiency of Recovery of Biotinylated mRNAs</u>

The efficiency of the recovery procedure was evaluated as follows. RNAs were labeled with ³²pCp, oxidized, biotinylated and bound to streptavidin coated beads as described above. Subsequently, the bound RNAs were incubated for 5, 15 or 30 minutes at 95°C in the presence of 2% SDS.

The products of the reaction were analyzed by electrophoresis on 12% polyacrylamide gels under denaturing 30 conditions (7 M urea). The gels were subjected to autoradiography. During this manipulation, the hydrazone bonds were not reduced.

Increasing amounts of nucleic acids were recovered as incubation times in 2% SDS increased, demonstrating that biotinylated mRNAs were efficiently recovered.

In an alternative method for obtaining mRNAs having intact 5' ends, an oligonucleotide which has been derivatized to contain a reactive amine group is specifically coupled to mRNAs having an intact cap. Preferably, the 3' end of the mRNA is blocked prior to the step in which the aldehyde groups are joined to the derivatized oligonucleotide, as described above, so as to prevent the derivatized oligonucleotide from being joined to the 3' end of the mRNA. For example, pCp may be attached to the 3' end of the mRNA using T4 RNA ligase. However, as discussed above, blocking the 3' end of the mRNA is an optional step. Derivatized oligonucleotides may be prepared as described below in Example 7.

EXAMPLE 7

Derivatization of the Oligonucleotide

An oligonucleotide phosphorylated at its 3' end was converted to a 3' hydrazide in 3' by treatment with an aqueous solution of hydrazine or of dihydrazide of the formula $H_2N(R1)NH_2$ at about 1 to 3 M, and at pH 4.5, in the presence of a carbodiimide type agent soluble in water such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide at a final concentration of 0.3 M at a temperature of 8°C overnight.

The derivatized oligonucleotide was then separated from the other agents and products using a standard technique for isolating oligonucleotides.

As discussed above, the mRNAs to be enriched may be treated to eliminate the 3' OH groups which may be present thereon. This may be accomplished by enzymatic ligation of sequences lacking a 3' OH, such as pCp, as described above in Example 1. Alternatively, the 3' OH groups may be eliminated by alkaline hydrolysis as described in Example 8 below.

20 EXAMPLE 8

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Alkaline Hydrolysis of mRNA

The mRNAs may be treated with alkaline hydrolysis as follows. In a total volume of 100µl of 0.1N sodium hydroxide, 1.5µg mRNA is incubated for 40 to 60 minutes at 4°C. The solution is neutralized with acetic acid and precipitated with ethanol.

Following the optional elimination of the 3' OH groups, the diol groups at the 5' ends of the mRNAs are oxidized as described below in Example 9.

EXAMPLE 9

Oxidation of Diols

Up to 1 OD unit of RNA was dissolved in 9 µl of buffer (0.1 M sodium acetate, pH 6-7 or water) and 3 µl of freshly prepared 0.1 M sodium periodate solution. The reaction was incubated for 1 h in the dark at 4°C or room temperature. Following the incubation, the reaction was stopped by adding 4 µl of 10% ethylene glycol. Thereafter the mixture was incubated at room temperature for 15 minutes. After ethanol precipitation, the product was resuspended in 10µl or more of water or appropriate buffer and dialyzed against water.

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Following oxidation of the diol groups at the 5' ends of the mRNAs, the derivatized oligonucleotide was joined to the resulting aldehydes as described in Example 10.

EXAMPLE 10

Reaction of Aldehydes with Derivatized Oligonucleotides

The oxidized mRNA was dissolved in an acidic medium such as 50 μl of sodium acetate pH 4-6. 50 μl of a solution of the derivatized oligonucleotide was added such that an mRNA:derivatized oligonucleotide ratio of 1:20 was obtained and mixture was reduced with a borohydride. The mixture was allowed to incubate for 2 h at 37°C or overnight (14 h) at 10°C. The mixture was ethanol precipitated, resuspended in 10μl or more of water or appropriate buffer and dialyzed against distilled water. If desired, the resulting product may be analyzed using acrylamide gel electrophoresis, HPLC analysis, or other conventional techniques.

Following the attachment of the derivatized oligonucleotide to the mRNAs, a reverse transcription reaction may be performed as described in Example 11 below.

EXAMPLE 11

Reverse Transcription of mRNAs

An oligodeoxyribonucleotide was derivatized as follows. 3 OD units of an oligodeoxyribonucleotide of sequence ATCAAGAATTCGCACGAGACCATTA (SEQ ID NO:3) having 5'-OH and 3'-P ends were dissolved in 70 µl of a 1.5 M hydroxybenzotriazole solution, pH 5.3, prepared in dimethylformamide/water (75:25) containing 2 µg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. The mixture was incubated for 2 h 30 min at 22°C. The mixture was then precipitated twice in LiClO₄/acetone. The pellet was resuspended in 200 µl of 0.25 M hydrazine and incubated at 8°C from 3 to 14 h. Following the hydrazine reaction, the mixture was precipitated twice in LiClO₄/acetone.

The messenger RNAs to be reverse transcribed were extracted from blocks of placenta having sides of 2 cm which had been stored at -80°C. The mRNA was extracted using conventional acidic phenol techniques. Oligo-dT chromatography was used to purify the mRNAs. The integrity of the mRNAs was checked by Northern-blotting.

The diol groups on 7 µg of the placental mRNAs were oxidized as described above in Example 9. The

derivatized oligonucleotide was joined to the mRNAs as described in Example 10 above except that the precipitation step
was replaced by an exclusion chromatography step to remove derivatized oligodeoxyribonucleotides which were not
joined to mRNAs. Exclusion chromatography was performed as follows:

10 ml of AcA34 (BioSepra#230151) gel were equilibrated in 50 ml of a solution of 10 mM Tris pH 8.0, 300 mM NaCl, 1 mM EDTA, and 0.05% SDS. The mixture was allowed to sediment. The supernatant was eliminated and the gel was resuspended in 50 ml of buffer. This procedure was repeated 2 or 3 times.

A glass bead (diameter 3 mm) was introduced into a 2 ml disposable pipette (length 25 cm). The pipette was filled with the gel suspension until the height of the gel stabilized at 1 cm from the top of the pipette. The column was then equilibrated with 20 ml of equilibration buffer (10 mM Tris HCl pH 7.4, 20 mM NaCl).

10 μ l of the mRNA which had been reacted with the derivatized oligonucleotide were mixed in 39 μ l of 10 mM urea and 2 μ l of blue-glycerol buffer, which had been prepared by dissolving 5 mg of bromophenol blue in 60% glycerol (v/v), and passing the mixture through a filter with a filter of diameter 0.45 μ m.

The column was loaded. As soon as the sample had penetrated, equilibration buffer was added. 100 µl

fractions were collected. Derivatized oligonucleotide which had not been attached to mRNA appeared in fraction 16 and later fractions. Fractions 3 to 15 were combined and precipitated with ethanol.

The mRNAs which had been reacted with the derivatized oligonucleotide were spotted on a nylon membrane and hybridized to a radioactive probe using conventional techniques. The radioactive probe used in these hybridizations was an oligodeoxyribonucleotide of sequence TAATGGTCTCGTGCGAATTCTTGAT (SEQ ID NO:4) which was anticomplementary to the derivatized oligonucleotide and was labeled at its 5' end with 32P. 1/10th of the mRNAs which had been reacted with the derivatized oligonucleotide was spotted in two spots on the membrane and the membrane was visualized by autoradiography after hybridization of the probe. A signal was observed, indicating that the derivatized oligonucleotide had been joined to the mRNA.

The remaining 9/10 of the mRNAs which had been reacted with the derivatized oligonucleotide was reverse transcribed as follows. A reverse transcription reaction was carried out with reverse transcriptase following the manufacturer's instructions. To prime the reaction, 50 pmol of nonamers with random sequence were used.

A portion of the resulting cDNA was spotted on a positively charged nylon membrane using conventional methods. The cDNAs were spotted on the membrane after the cDNA:RNA heteroduplexes had been subjected to an alkaline hydrolysis in order to eliminate the RNAs. An oligonucleotide having a sequence identical to that of the derivatized oligonucleotide was labeled at its 5' end with ³²P and hybridized to the cDNA blots using conventional techniques. Single-stranded cDNAs resulting from the reverse transcription reaction were spotted on the membrane. As controls, the blot contained 1 pmol, 100 fmol, 50 fmol, 10 fmol and 1 fmol respectively of a control oligodeoxyribonucleotide of sequence identical to that of the derivatized oligonucleotide. The signal observed in the spots containing the cDNA indicated that approximately 15 fmol of the derivatized oligonucleotide had been reverse transcribed.

These results demonstrate that the reverse transcription can be performed through the cap and, in particular, that reverse transcriptase crosses the 5'-P-P-5' bond of the cap of eukaryotic messenger RNAs.

The single stranded cDNAs obtained after the above first strand synthesis were used as template for PCR reactions. Two types of reactions were carried out. First, specific amplification of the mRNAs for the alpha globin, dehydrogenase, pp15 and elongation factor E4 were carried out using the following pairs of oligodeoxyribonucleotide primers.

alpha-globin

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GLO-S: CCG ACA AGA CCA ACG TCA AGG CCG C (SEQ ID NO:5)

GLO-As: TCA CCA GCA GGC AGT GGC TTA GGA G 3' (SEQ ID NO:6)

dehydrogenase

3 DH-S: AGT GAT TCC TGC TAC TTT GGA TGG C (SEQ ID NO:7)

3 DH-As: GCT TGG TCT TGT TCT GGA GTT TAG A (SEQ ID NO:8)

pp15

PP15-S: TCC AGA ATG GGA GAC AAG CCA ATT T (SEQ ID NO:9)

5 PP15-As: AGG GAG GAG GAA ACA GCG TGA GTC C (SEQ ID NO:10)

Elongation factor E4

EFA1-S: ATG GGA AAG GAA AAG ACT CAT ATC A (SEQ ID NO:11)

EF1A-As: AGC AGC AAC AAT CAG GAC AGC ACA G (SEQ ID NO:12)

Non specific amplifications were also carried out with the antisense (_As) oligodeoxyribonucleotides of the pairs described above and a primer chosen from the sequence of the derivatized oligodeoxyribonucleotide (ATCAAGAATTCGCACGAGACCATTA) (SEQ ID NO:13).

A 1.5% agarose gel containing the following samples corresponding to the PCR products of reverse transcription was stained with ethidium bromide. (1/20th of the products of reverse transcription were used for each PCR reaction).

- Sample 1: The products of a PCR reaction using the globin primers of SEQ ID NOs 5 and 6 in the presence of cDNA.
 - Sample 2: The products of a PCR reaction using the globin primers of SEQ ID NOs 5 and 6 in the absence of added cDNA.
- Sample 3: The products of a PCR reaction using the dehydrogenase primers of SEQ ID NOs 7 and 8 in the 20 presence of cDNA.
 - Sample 4: The products of a PCR reaction using the dehydrogenase primers of SEQ ID NOs 7 and 8 in the absence of added cDNA.
 - Sample 5: The products of a PCR reaction using the pp15 primers of SEQ ID NOs 9 and 10 in the presence of cDNA.
- Sample 6: The products of a PCR reaction using the pp15 primers of SEQ ID NOs 9 and 10 in the absence of added cDNA.
 - Sample 7: The products of a PCR reaction using the EIE4 primers of SEQ ID NOs 11 and 12 in the presence of added cDNA.
- Sample 8: The products of a PCR reaction using the EIE4 primers of SEQ ID NOs 11 and 12 in the absence of 30 added cDNA.

In Samples 1, 3, 5 and 7, a band of the size expected for the PCR product was observed, indicating the presence of the corresponding sequence in the cDNA population.

PCR reactions were also carried out with the antisense oligonucleotides of the globin and dehydrogenase primers (SEO ID NOs 6 and 8) and an oligonucleotide whose sequence corresponds to that of the derivatized

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oligonucleotide. The presence of PCR products of the expected size in the samples corresponding to samples 1 and 3 above indicated that the derivatized oligonucleotide had been incorporated.

The above examples summarize the chemical procedure for enriching mRNAs for those having intact 5' ends.

Further detail regarding the chemical approaches for obtaining mRNAs having intact 5' ends are disclosed in

International Application No. W096/34981, published November 7, 1996.

Strategies based on the above chemical modifications to the 5' cap structure may be utilized to generate cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived. In one version of such procedures, the 5' ends of the mRNAs are modified as described above. Thereafter, a reverse transcription reaction is conducted to extend a primer complementary to the mRNA to the 5' end of the mRNA. Single stranded RNAs are eliminated to obtain a population of cDNA/mRNA heteroduplexes in which the mRNA includes an intact 5' end. The resulting heteroduplexes may be captured on a solid phase coated with a molecule capable of interacting with the molecule used to derivatize the 5' end of the mRNA. Thereafter, the strands of the heteroduplexes are separated to recover single stranded first cDNA strands which include the 5' end of the mRNA. Second strand cDNA synthesis may then proceed using conventional techniques. For example, the procedures disclosed in WO 96/34981 or in Carninci, P. et al. High-Efficiency Full-Length cDNA Cloning by Biotinylated CAP Trapper. Genomics 37:327-336 (1996) may be employed to select cDNAs which include the sequence derived from the 5' end of the coding sequence of the mRNA.

Following ligation of the oligonucleotide tag to the 5' cap of the mRNA, a reverse transcription reaction is conducted to extend a primer complementary to the mRNA to the 5' end of the mRNA. Following elimination of the RNA component of the resulting heteroduplex using standard techniques, second strand cDNA synthesis is conducted with a primer complementary to the oligonucleotide tag.

Figure 1 summarizes the above procedures for obtaining cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived.

B. Enzymatic Methods for Obtaining mRNAs having Intact 5' Ends

Other techniques for selecting cDNAs extending to the 5' end of the mRNA from which they are derived are fully enzymatic. Some versions of these techniques are disclosed in Dumas Milne Edwards J.B. (Doctoral Thesis of Paris VI University, Le clonage des ADNc complets: difficultes et perspectives nouvelles. Apports pour l'etude de la regulation de l'expression de la tryptophane hydroxylase de rat, 20 Dec. 1993), EPO 625572 and Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994).

Briefly, in such approaches, isolated mRNA is treated with alkaline phosphatase to remove the phosphate

groups present on the 5' ends of uncapped incomplete mRNAs. Following this procedure, the cap present on full length mRNAs is enzymatically removed with a decapping enzyme such as T4 polynucleotide kinase or tobacco acid pyrophosphatase. An oligonucleotide, which may be either a DNA oligonucleotide or a DNA-RNA hybrid oligonucleotide having RNA at its 3' end, is then ligated to the phosphate present at the 5' end of the decapped mRNA using T4 RNA

ligase. The oligonucleotide may include a restriction site to facilitate cloning of the cDNAs following their synthesis. Example 12 below describes one enzymatic method based on the doctoral thesis of Dumas.

EXAMPLE 12

Enzymatic Approach for Obtaining 5' ESTs

Twenty micrograms of PolyA + RNA were dephosphorylated using Calf Intestinal Phosphatase (Biolabs). After a phenol chloroform extraction, the cap structure of mRNA was hydrolysed using the Tobacco Acid Pyrophosphatase (purified as described by Shinshi et al., Biochemistry 15: 2185-2190, 1976) and a hemi 5'DNA/RNA-3' oligonucleotide having an unphosphorylated 5' end, a stretch of adenosine ribophosphate at the 3' end, and an EcoRI site near the 5' end was ligated to the 5'P ends of mRNA using the T4 RNA ligase (Biolabs). Oligonucleotides suitable for use in this 10 procedure are preferably 30-50 bases in length. Oligonucleotides having an unphosphorylated 5' end may be synthesized by adding a fluorochrome at the 5' end. The inclusion of a stretch of adenosine ribophosphates at the 3' end of the oligonucleotide increases ligation efficiency. It will be appreciated that the oligonucleotide may contain cloning sites other than EcoRI.

Following ligation of the oligonucleotide to the phosphate present at the 5' end of the decapped mRNA, first 15 and second strand cDNA synthesis may be carried out using conventional methods or those specified in EPO 625,572 and Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994), and Dumas Milne Edwards, supra. The resulting cDNA may then be ligated into vectors such as those disclosed in Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994) or other nucleic acid vectors known to those skilled in the art using techniques such as those described in Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold 20 Spring Harbor Laboratory Press, 1989.

II. Characterization of 5' ESTs

The above chemical and enzymatic approaches for enriching mRNAs having intact 5' ends were employed to obtain 5' ESTs. First, mRNAs were prepared as described in Example 13 below.

EXAMPLE 13

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Preparation of mRNA

Total human RNAs or PolyA + RNAs derived from 29 different tissues were respectively purchased from LABIMO and CLONTECH and used to generate 44 cDNA libraries as described below. The purchased RNA had been isolated from cells or tissues using acid guanidium thiocyanate-phenol-chloroform extraction (Chomczyniski, P and Sacchi, N., Analytical Biochemistry 162:156-159, 1987). PolyA+ RNA was isolated from total RNA (LABIMO) by 30 two passes of oligodT chromatography, as described by Aviv and Leder (Aviv, H. and Leder, P., Proc. Natl. Acad. Sci. USA 69:1408-1412, 1972) in order to eliminate ribosomal RNA.

The quality and the integrity of the poly A+ were checked. Northern blots hybridized with a globin probe were used to confirm that the mRNAs were not degraded. Contamination of the PolyA+ mRNAs by ribosomal sequences was checked using RNAs blots and a probe derived from the sequence of the 28S RNA. Preparations of mRNAs with less

than 5% of ribosomal RNAs were used in library construction. To avoid constructing libraries with RNAs contaminated by exogenous sequences (prokaryotic or fungal), the presence of bacterial 16S ribosomal sequences or of two highly expressed mRNAs was examined using PCR.

Following preparation of the mRNAs, the above described chemical and/or the enzymatic procedures for enriching mRNAs having intact 5' ends discussed above were employed to obtain 5' ESTs from various tissues. In both approaches an oligonucleotide tag was attached to the cap at the 5' ends of the mRNAs. The oligonucleotide tag had an EcoRI site therein to facilitate later cloning procedures.

Following attachment of the oligonucleotide tag to the mRNA by either the chemical or enzymatic methods, the integrity of the mRNA was examined by performing a Northern blot with 200-500ng of mRNA using a probe complementary to the oligonucleotide tag.

EXAMPLE 14

cDNA Synthesis Using mRNA Templates Having Intact 5' Ends

For the mRNAs joined to oligonucleotide tags using both the chemical and enzymatic methods, first strand cDNA synthesis was performed using reverse transcriptase with random nonamers as primers. In order to protect internal EcoRI sites in the cDNA from digestion at later steps in the procedure, methylated dCTP was used for first strand synthesis. After removal of RNA by an alkaline hydrolysis, the first strand of cDNA was precipitated using isopropanol in order to eliminate residual primers.

For both the chemical and the enzymatic methods, the second strand of the cDNA was synthesized with a Klenow fragment using a primer corresponding to the 5'end of the ligated oligonucleotide described in Example 12.

Preferably, the primer is 20-25 bases in length. Methylated dCTP was also used for second strand synthesis in order to protect internal EcoRI sites in the cDNA from digestion during the cloning process.

Following cDNA synthesis, the cDNAs were cloned into pBlueScript as described in Example 15 below.

EXAMPLE 15

Insertion of cDNAs into BlueScript

Following second strand synthesis, the ends of the cDNA were blunted with T4 DNA polymerase (Biolabs) and the cDNA was digested with EcoRI. Since methylated dCTP was used during cDNA synthesis, the EcoRI site present in the tag was the only site which was hemi-methylated. Consequently, only the EcoRI site in the oligonucleotide tag was susceptible to EcoRI digestion. The cDNA was then size fractionated using exclusion chromatography (AcA, Biosepra). Fractions corresponding to cDNAs of more than 150 bp were pooled and ethanol precipitated. The cDNA was directionally cloned into the Smal and EcoRI ends of the phagemid pBlueScript vector (Stratagene). The ligation mixture was electroporated into bacteria and propagated under appropriate antibiotic selection.

Clones containing the oligonucleotide tag attached were selected as described in Example 16 below.

EXAMPLE 16

Selection of Clones Having the Oligonucleotide Tag Attached Thereto

The plasmid DNAs containing 5' EST libraries made as described above were purified (Qiagen). A positive selection of the tagged clones was performed as follows. Briefly, in this selection procedure, the plasmid DNA was converted to single stranded DNA using gene II endonuclease of the phage F1 in combination with an exonuclease (Chang et al., Gene 127:95-8, 1993) such as exonuclease III or T7 gene 6 exonuclease. The resulting single stranded DNA was then purified using paramagnetic beads as described by Fry et al., Biotechniques, 13: 124-131, 1992. In this procedure, the single stranded DNA was hybridized with a biotinylated oligonucleotide having a sequence corresponding to the 3' end of the oligonucleotide described in Example 13. Preferably, the primer has a length of 20-25 bases. Clones including a sequence complementary to the biotinylated oligonucleotide were captured by incubation with streptavidin coated magnetic beads followed by magnetic selection. After capture of the positive clones, the plasmid DNA was released from the magnetic beads and converted into double stranded DNA using a DNA polymerase such as the ThermoSequenase obtained from Amersham Pharmacia Biotech. Alternatively, protocols such as the Gene Trapper kit (Gibco BRL) may be used. The double stranded DNA was then electroporated into bacteria. The percentage of positive clones having the 5' tag oligonucleotide was estimated to typically rank between 90 and 98% using dot blot analysis.

Following electroporation, the libraries were ordered in 384-microtiter plates (MTP). A copy of the MTP was stored for future needs. Then the libraries were transferred into 96 MTP and sequenced as described below.

EXAMPLE 17

Sequencing of Inserts in Selected Clones

Plasmid inserts were first amplified by PCR on PE 9600 thermocyclers (Perkin-Elmer), using standard SETA-A and SETA-B primers (Genset SA), AmpliTaqGold (Perkin-Elmer), dNTPs (Boehringer), buffer and cycling conditions as recommended by the Perkin-Elmer Corporation.

PCR products were then sequenced using automatic ABI Prism 377 sequencers (Perkin Elmer, Applied Biosystems Division, Foster City, CA). Sequencing reactions were performed using PE 9600 thermocyclers (Perkin Elmer) with standard dye-primer chemistry and ThermoSequenase (Amersham Life Science). The primers used were either T7 or 21M13 (available from Genset SA) as appropriate. The primers were labeled with the JOE, FAM, ROX and TAMRA dyes. The dNTPs and ddNTPs used in the sequencing reactions were purchased from Boehringer. Sequencing buffer, reagent concentrations and cycling conditions were as recommended by Amersham.

Following the sequencing reaction, the samples were precipitated with EtOH, resuspended in formamide loading buffer, and loaded on a standard 4% acrylamide gel. Electrophoresis was performed for 2.5 hours at 3000V on an ABI 377 sequencer, and the sequence data were collected and analyzed using the ABI Prism DNA Sequencing Analysis Software, version 2.1.2.

The sequence data from the 44 cDNA libraries made as described above were transferred to a proprietary database, where quality control and validation steps were performed. A proprietary base-caller ("Trace"), working using a Unix system automatically flagged suspect peaks, taking into account the shape of the peaks, the inter-peak resolution, and the noise level. The proprietary base-caller also performed an automatic trimming. Any stretch of 25 or

fewer bases having more than 4 suspect peaks was considered unreliable and was discarded. Sequences corresponding to cloning vector or ligation oligonucleotides were automatically removed from the EST sequences. However, the resulting EST sequences may contain 1 to 5 bases belonging to the above mentioned sequences at their 5' end. If needed, these can easily be removed on a case by case basis.

5 Thereafter, the sequences were transferred to the proprietary NETGENE™ Database for further analysis as described below.

Following sequencing as described above, the sequences of the 5' ESTs were entered in a proprietary database called NETGENETM for storage and manipulation. It will be appreciated by those skilled in the art that the data could be stored and manipulated on any medium which can be read and accessed by a computer. Computer readable media include magnetically readable media, optically readable media, or electronically readable media. For example, the computer readable media may be a hard disc, a floppy disc, a magnetic tape, CD-ROM, RAM, or ROM as well as other types of other media known to those skilled in the art.

In addition, the sequence data may be stored and manipulated in a variety of data processor programs in a variety of formats. For example, the sequence data may be stored as text in a word processing file, such as

MicrosoftWORD or WORDPERFECT or as an ASCII file in a variety of database programs familiar to those of skill in the art, such as DB2, SYBASE, or ORACLE.

The computer readable media on which the sequence information is stored may be in a personal computer, a network, a server or other computer systems known to those skilled in the art. The computer or other system preferably includes the storage media described above, and a processor for accessing and manipulating the sequence data.

Once the sequence data has been stored it may be manipulated and searched to locate those stored sequences which contain a desired nucleic acid sequence or which encode a protein having a particular functional domain. For example, the stored sequence information may be compared to other known sequences to identify homologies, motifs implicated in biological function, or structural motifs.

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Programs which may be used to search or compare the stored sequences include the MacPattern (EMBL),

25 BLAST, and BLAST2 program series (NCBI), basic local alignment search tool programs for nucleotide (BLASTN) and
peptide (BLASTX) comparisons (Altschul et al, J. Mol. Biol. 215: 403 (1990)) and FASTA (Pearson and Lipman, Proc.

Natl. Acad. Sci. USA, 85: 2444 (1988)). The BLAST programs then extend the alignments on the basis of defined
match and mismatch criteria.

Motifs which may be detected using the above programs include sequences encoding leucine zippers, helix-turn30 helix motifs, glycosylation sites, ubiquitination sites, alpha helices, and beta sheets, signal sequences encoding signal peptides which direct the secretion of the encoded proteins, sequences implicated in transcription regulation such as homeoboxes, acidic stretches, enzymatic active sites, substrate binding sites, and enzymatic cleavage sites.

Before searching the cDNAs in the NETGENE™ database for sequence motifs of interest, cDNAs derived from mRNAs which were not of interest were identified and eliminated from further consideration as described in Example 18 below.

EXAMPLE 18

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Elimination of Undesired Sequences from Further Consideration

5' ESTs in the NETGENETM database which were derived from undesired sequences such as transfer RNAs, ribosomal RNAs, mitochondrial RNAs, procaryotic RNAs, fungal RNAs, Alu sequences, L1 sequences, or repeat sequences were identified using the FASTA and BLASTN programs with the parameters listed in Table II.

To eliminate 5' ESTs encoding tRNAs from further consideration, the 5' EST sequences were compared to the 10 sequences of 1190 known tRNAs obtained from EMBL release 38, of which 100 were human. The comparison was performed using FASTA on both strands of the 5' ESTs. Sequences having more than 80% homology over more than 60 nucleotides were identified as tRNA. Of the 144,341 sequences screened, 26 were identified as tRNAs and eliminated from further consideration.

To eliminate 5' ESTs encoding rRNAs from further consideration, the 5' EST sequences were compared to the 15 sequences of 2497 known rRNAs obtained from EMBL release 38, of which 73 were human. The comparison was performed using BLASTN on both strands of the 5' ESTs with the parameter S = 108. Sequences having more than 80% homology over stretches longer than 40 nucleotides were identified as rRNAs. Of the 144,341 sequences screened, 3,312 were identified as rRNAs and eliminated from further consideration.

To eliminate 5' ESTs encoding mtRNAs from further consideration, the 5' EST sequences were compared to 20 the sequences of the two known mitochondrial genomes for which the entire genomic sequences are available and all sequences transcribed from these mitochondrial genomes including tRNAs, rRNAs, and mRNAs for a total of 38 sequences. The comparison was performed using BLASTN on both strands of the 5' ESTs with the parameter S=108. Sequences having more than 80% homology over stretches longer than 40 nucleotides were identified as mtRNAs. Of the 144,341 sequences screened, 6,110 were identified as mtRNAs and eliminated from further consideration.

Sequences which might have resulted from exogenous contaminants were eliminated from further consideration by comparing the 5' EST sequences to release 46 of the EMBL bacterial and fungal divisions using BLASTN with the parameter S = 144. All sequences having more than 90% homology over at least 40 nucleotides were identified as exogenous contaminants. Of the 42 cDNA libraries examined, the average percentages of procaryotic and fungal sequences contained therein were 0.2% and 0.5% respectively. Among these sequences, only one could be 30 identified as a sequence specific to fungi. The others were either fungal or procaryotic sequences having homologies with vertebrate sequences or including repeat sequences which had not been masked during the electronic comparison.

In addition, the 5' ESTs were compared to 6093 Alu sequences and 1115 L1 sequences to mask 5' ESTs containing such repeat sequences from further consideration. 5' ESTs including THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats were also eliminated from further consideration. On average, 11.5% of

the sequences in the libraries contained repeat sequences. Of this 11.5%, 7% contained Alu repeats, 3.3% contained £1 repeats and the remaining 1.2% were derived from the other types of repetitive sequences which were screened. These percentages are consistent with those found in cDNA libraries prepared by other groups. For example, the cDNA libraries of Adams et al. contained between 0% and 7.4% Alu repeats depending on the source of the RNA which was used to prepare the cDNA library (Adams et al., *Nature* 377:174, 1996).

The sequences of those 5' ESTs remaining after the elimination of undesirable sequences were compared with the sequences of known human mRNAs to determine the accuracy of the sequencing procedures described above.

EXAMPLE 19

Measurement of Sequencing Accuracy by Comparison to Known Sequences

To further determine the accuracy of the sequencing procedure described above, the sequences of 5' ESTs derived from known sequences were identified and compared to the known sequences. First, a FASTA analysis with overhangs shorter than 5 bp on both ends was conducted on the 5' ESTs to identify those matching an entry in the public human mRNA database. The 6655 5' ESTs which matched a known human mRNA were then realigned with their cognate mRNA and dynamic programming was used to include substitutions, insertions, and deletions in the list of "errors" which would be recognized. Errors occurring in the last 10 bases of the 5' EST sequences were ignored to avoid the inclusion of spurious cloning sites in the analysis of sequencing accuracy.

This analysis revealed that the sequences incorporated in the NETGENETM database had an accuracy of more than 99.5%.

To determine the efficiency with which the above selection procedures select cDNAs which include the 5' ends of their corresponding mRNAs, the following analysis was performed.

EXAMPLE 20

Determination of Efficiency of 5' EST Selection

To determine the efficiency at which the above selection procedures isolated 5' ESTs which included sequences close to the 5' end of the mRNAs from which they were derived, the sequences of the ends of the 5' ESTs which were derived from the elongation factor 1 subunit α and ferritin heavy chain genes were compared to the known cDNA sequences for these genes. Since the transcription start sites for the elongation factor 1 subunit α and ferritin heavy chain are well characterized, they may be used to determine the percentage of 5' ESTs derived from these genes which included the authentic transcription start sites.

For both genes, more than 95% of the cDNAs included sequences close to or upstream of the 5' end of the corresponding mRNAs.

To extend the analysis of the reliability of the procedures for isolating 5' ESTs from ESTs in the NETGENETM database, a similar analysis was conducted using a database composed of human mRNA sequences extracted from GenBank database release 97 for comparison. For those 5' ESTs derived from mRNAs included in the GeneBank database, more than 85% had their 5' ends close to the 5' ends of the known sequence. As some of the mRNA

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sequences available in the GenBank database are deduced from genomic sequences, a 5' end matching with these sequences will be counted as an internal match. Thus, the method used here underestimates the yield of ESTs including the authentic 5' ends of their corresponding mRNAs.

The EST libraries made above included multiple 5' ESTs derived from the same mRNA. The sequences of such 5' ESTs were compared to one another and the longest 5' ESTs for each mRNA were identified. Overlapping cDNAs were assembled into continuous sequences (contigs). The resulting continuous sequences were then compared to public databases to gauge their similarity to known sequences, as described in Example 21 below.

EXAMPLE 21

Clustering of the 5' ESTs and Calculation of Novelty Indices for cDNA Libraries

For each sequenced EST library, the sequences were clustered by the 5' end. Each sequence in the library was compared to the others with BLASTN2 (direct strand, parameters S = 107). ESTs with High Scoring Segment Pairs (HSPs) at least 25 bp long, having 95% identical bases and beginning closer than 10 bp from each EST 5' end were grouped. The longest sequence found in the cluster was used as representative of the cluster. A global clustering between libraries was then performed leading to the definition of super-contigs.

To assess the yield of new sequences within the EST libraries, a novelty rate (NR) was defined as: NR = 100 X (Number of new unique sequences found in the library/Total number of sequences from the library). Typically, novelty rating range between 10% and 41% depending on the tissue from which the EST library was obtained. For most of the libraries, the random sequencing of 5' EST libraries was pursued until the novelty rate reached 20%.

Following characterization as described above, the collection of 5' ESTs in NETGENETM was screened to 20 identify those 5' ESTs bearing potential signal sequences as described in Example 22 below.

EXAMPLE 22

Identification of Potential Signal Sequences in 5' ESTs

The 5' ESTs in the NETGENETM database were screened to identify those having an uninterrupted open reading frame (ORF) longer than 45 nucleotides beginning with an ATG codon and extending to the end of the EST.

25 Approximately half of the cDNA sequences in NETGENETM contained such an ORF. The ORFs of these 5' ESTs were searched to identify potential signal motifs using slight modifications of the procedures disclosed in Von Heijne, G. A New Method for Predicting Signal Sequence Cleavage Sites. Nucleic Acids Res. 14:4683-4690 (1986). Those 5' EST sequences encoding a 15 amino acid long stretch with a score of at least 3.5 in the Von Heijne signal peptide identification matrix were considered to possess a signal sequence. Those 5' ESTs which matched a known human mRNA or EST sequence and had a 5' end more than 20 nucleotides downstream of the known 5' end were excluded from further analysis. The remaining cDNAs having signal sequences therein were included in a database called SIGNALTAGTM.

To confirm the accuracy of the above method for identifying signal sequences, the analysis of Example 23 was performed.

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EXAMPLE 23

Confirmation of Accuracy of Identification of Potential Signal Sequences in 5' ESTs

The accuracy of the above procedure for identifying signal sequences encoding signal peptides was evaluated by applying the method to the 43 amino terminal amino acids of all human SwissProt proteins. The computed Von Heijne score for each protein was compared with the known characterization of the protein as being a secreted protein or a non-secreted protein. In this manner, the number of non-secreted proteins having a score higher than 3.5 (false positives) and the number of secreted proteins having a score lower than 3.5 (false negatives) could be calculated.

Using the results of the above analysis, the probability that a peptide encoded by the 5' region of the mRNA is in fact a genuine signal peptide based on its Von Heijne's score was calculated based on either the assumption that 10% of human proteins are secreted or the assumption that 20% of human proteins are secreted. The results of this analysis are shown in Figures 2 and 3.

Using the above method of identifying secretory proteins, 5' ESTs for human glucagon, gamma interferon induced monokine precursor, secreted cyclophilin-like protein, human pleiotropin, and human biotinidase precursor all of which are polypeptides which are known to be secreted, were obtained. Thus, the above method successfully identified those 5' ESTs which encode a signal peptide.

To confirm that the signal peptide encoded by the 5' ESTs actually functions as a signal peptide, the signal sequences from the 5' ESTs may be cloned into a vector designed for the identification of signal peptides. Some signal peptide identification vectors are designed to confer the ability to grow in selective medium on host cells which have a signal sequence operably inserted into the vector. For example, to confirm that a 5' EST encodes a genuine signal peptide, the signal sequence of the 5' EST may be inserted upstream and in frame with a non-secreted form of the yeast invertase gene in signal peptide selection vectors such as those described in U.S. Patent No. 5,536,637. Growth of host cells containing signal sequence selection vectors having the signal sequence from the 5' EST inserted therein confirms that the 5' EST encodes a genuine signal peptide.

Alternatively, the presence of a signal peptide may be confirmed by cloning the extended cDNAs obtained using
the ESTs into expression vectors such as pXT1 (as described below), or by constructing promoter-signal sequencereporter gene vectors which encode fusion proteins between the signal peptide and an assayable reporter protein. After
introduction of these vectors into a suitable host cell, such as COS cells or NIH 3T3 cells, the growth medium may be
harvested and analyzed for the presence of the secreted protein. The medium from these cells is compared to the
medium from cells containing vectors lacking the signal sequence or extended cDNA insert to identify vectors which
encode a functional signal peptide or an authentic secreted protein.

Those 5' ESTs which encoded a signal peptide, as determined by the method of Example 22 above, were further grouped into four categories based on their homology to known sequences. The categorization of the 5' ESTs is described in Example 24 below.

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Categorization of 5' ESTs Encoding a Signal Peptide

Those 5' ESTs having a sequence not matching any known vertebrate sequence nor any publicly available EST sequence were designated "new." Of the sequences in the SIGNALTAGTM database, 947 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

5 Those 5' ESTs having a sequence not matching any vertebrate sequence but matching a publicly known EST were designated "EST-ext", provided that the known EST sequence was extended by at least 40 nucleotides in the 5' direction. Of the sequences in the SIGNALTAGTM database, 150 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those ESTs not matching any vertebrate sequence but matching a publicly known EST without extending the 10 known EST by at least 40 nucleotides in the 5' direction were designated "EST." Of the sequences in the SIGNALTAG™ database, 599 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those 5' ESTs matching a human mRNA sequence but extending the known sequence by at least 40 nucleotides in the 5' direction were designated "VERT-ext." Of the sequences in the SIGNALTAG™ database, 23 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category. Included in this category was a 5' EST which 15 extended the known sequence of the human translocase mRNA by more than 200 bases in the 5' direction. A 5' EST which extended the sequence of a human tumor suppressor gene in the 5' direction was also identified.

Figure 4 shows the distribution of 5' ESTs in each category and the number of 5' ESTs in each category having a given minimum von Heijne's score.

Each of the 5' ESTs was categorized based on the tissue from which its corresponding mRNA was obtained, as described below in Example 25. 20

EXAMPLE 25

Categorization of Expression Patterns

Figure 5 shows the tissues from which the mRNAs corresponding to the 5' ESTs in each of the above described categories were obtained.

In addition to categorizing the 5' ESTs by the tissue from which the cDNA library in which they were first identified was obtained, the spatial and temporal expression patterns of the mRNAs corresponding to the 5' ESTs, as well as their expression levels, may be determined as described in Example 26 below. Characterization of the spatial and temporal expression patterns and expression levels of these mRNAs is useful for constructing expression vectors capable of producing a desired level of gene product in a desired spatial or temporal manner, as will be discussed in more detail 30 below.

In addition, 5' ESTs whose corresponding mRNAs are associated with disease states may also be identified. For example, a particular disease may result from lack of expression, over expression, or under expression of an mRNA corresponding to a 5' EST. By comparing mRNA expression patterns and quantities in samples taken from healthy

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individuals with those from individuals suffering from a particular disease, 5' ESTs responsible for the disease may be identified.

It will be appreciated that the results of the above characterization procedures for 5' ESTs also apply to extended cDNAs (obtainable as described below) which contain sequences adjacent to the 5' ESTs. It will also be appreciated that if it is desired to defer characterization until extended cDNAs have been obtained rather than characterizing the ESTs themselves, the above characterization procedures can be applied to characterize the extended cDNAs after their isolation.

EXAMPLE 26

Evaluation of Expression Levels and Patterns of mRNAs

Corresponding to 5' ESTs or Extended cDNAs

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Expression levels and patterns of mRNAs corresponding to 5' ESTs or extended cDNAs (obtainable as described below) may be analyzed by solution hybridization with long probes as described in International Patent Application No. WO 97/05277. Briefly, a 5' EST, extended cDNA, or fragment thereof corresponding to the gene encoding the mRNA to be characterized is inserted at a cloning site immediately downstream of a bacteriophage (T3, T7 or SP6) RNA polymerase promoter to produce antisense RNA. Preferably, the 5' EST or extended cDNA has 100 or more nucleotides. The plasmid is linearized and transcribed in the presence of ribonucleotides comprising modified ribonucleotides (i.e. biotin-UTP and DIG-UTP). An excess of this doubly labeled RNA is hybridized in solution with mRNA isolated from cells or tissues of interest. The hybridizations are performed under standard stringent conditions (40-50°C for 16 hours in an 80% formamide, 0.4 M NaCl buffer, pH 7-8). The unhybridized probe is removed by digestion with ribonucleases specific for single-stranded RNA (i.e. RNases CL3, T1, Phy M, U2 or A). The presence of the biotin-UTP modification enables capture of the hybrid on a microtitration plate coated with streptavidin. The presence of the DIG modification enables the hybrid to be detected and quantified by ELISA using an anti-DIG antibody coupled to alkaline phosphatase.

The 5' ESTs, extended cDNAs, or fragments thereof may also be tagged with nucleotide sequences for the serial analysis of gene expression (SAGE) as disclosed in UK Patent Application No. 2 305 241 A. In this method, cDNAs are prepared from a cell, tissue, organism or other source of nucleic acid for which it is desired to determine gene expression patterns. The resulting cDNAs are separated into two pools. The cDNAs in each pool are cleaved with a first restriction endonuclease, called an "anchoring enzyme," having a recognition site which is likely to be present at least once in most cDNAs. The fragments which contain the 5' or 3' most region of the cleaved cDNA are isolated by binding to a capture medium such as streptavidin coated beads. A first oligonucleotide linker having a first sequence for hybridization of an amplification primer and an internal restriction site for a "tagging endonuclease" is ligated to the digested cDNAs in the first pool. Digestion with the second endonuclease produces short "tag" fragments from the cDNAs.

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A second oligonucleotide having a second sequence for hybridization of an amplification primer and an internalrestriction site is ligated to the digested cDNAs in the second pool. The cDNA fragments in the second pool are also digested with the "tagging endonuclease" to generate short "tag" fragments derived from the cDNAs in the second pool. The "tags" resulting from digestion of the first and second pools with the anchoring enzyme and the tagging 5 endonuclease are ligated to one another to produce "ditags." In some embodiments, the ditags are concatamerized to produce ligation products containing from 2 to 200 ditags. The tag sequences are then determined and compared to the sequences of the 5' ESTs or extended cDNAs to determine which 5' ESTs or extended cDNAs are expressed in the cell, tissue, organism, or other source of nucleic acids from which the tags were derived. In this way, the expression pattern of the 5' ESTs or extended cDNAs in the cell, tissue, organism, or other source of nucleic acids is obtained.

Quantitative analysis of gene expression may also be performed using arrays. As used herein, the term array means a one dimensional, two dimensional, or multidimensional arrangement of full length cDNAs (i.e. extended cDNAs which include the coding sequence for the signal peptide, the coding sequence for the mature protein, and a stop codon), extended cDNAs, 5' ESTs or fragments of the full length cDNAs, extended cDNAs, or 5' ESTs of sufficient length to permit specific detection of gene expression. Preferably, the fragments are at least 15 nucleotides in length. More 15 preferably, the fragments are at least 100 nucleotides in length. More preferably, the fragments are more than 100 nucleotides in length. In some embodiments the fragments may be more than 500 nucleotides in length.

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For example, quantitative analysis of gene expression may be performed with full length cDNAs, extended cDNAs, 5' ESTs, or fragments thereof in a complementary DNA microarray as described by Schena et al. (Science 270:467-470, 1995; Proc. Natl. Acad. Sci. U.S.A. 93:10614-10619, 1996). Full length cDNAs, extended cDNAs, 5' 20 ESTs or fragments thereof are amplified by PCR and arrayed from 96-well microtiter plates onto silylated microscope slides using high-speed robotics. Printed arrays are incubated in a humid chamber to allow rehydration of the array elements and rinsed, once in 0.2% SDS for 1 min, twice in water for 1 min and once for 5 min in sodium borohydride solution. The arrays are submerged in water for 2 min at 95°C, transferred into 0.2% SDS for 1 min, rinsed twice with water, air dried and stored in the dark at 25°C.

Cell or tissue mRNA is isolated or commercially obtained and probes are prepared by a single round of reverse transcription. Probes are hybridized to 1 cm² microarrays under a 14 x 14 mm glass coverslip for 6-12 hours at 60°C. Arrays are washed for 5 min at 25°C in low stringency wash buffer (1 x SSC/0.2% SDS), then for 10 min at room temperature in high stringency wash buffer (0.1 x SSC/0.2% SDS). Arrays are scanned in 0.1 x SSC using a fluorescence laser scanning device fitted with a custom filter set. Accurate differential expression measurements are 30 obtained by taking the average of the ratios of two independent hybridizations.

Quantitative analysis of the expression of genes may also be performed with full length cDNAs, extended cDNAs, 5' ESTs, or fragments thereof in complementary DNA arrays as described by Pietu et al. (Genome Research 6:492-503, 1996). The full length cDNAs, extended cDNAs, 5' ESTs or fragments thereof are PCR amplified and spotted on membranes. Then, mRNAs originating from various tissues or cells are labeled with radioactive nucleotides.

After hybridization and washing in controlled conditions, the hybridized mRNAs are detected by phospho-imaging or autoradiography. Duplicate experiments are performed and a quantitative analysis of differentially expressed mRNAs is then performed.

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Alternatively, expression analysis of the 5' ESTs or extended cDNAs can be done through high density

nucleotide arrays as described by Lockhart et al. (Nature Biotechnology 14: 1675-1680, 1996) and Sosnowsky et al.

(Proc. Natl. Acad. Sci. 94:1119-1123, 1997). Oligonucleotides of 15-50 nucleotides corresponding to sequences of the 5' ESTs or extended cDNAs are synthesized directly on the chip (Lockhart et al., supra) or synthesized and then addressed to the chip (Sosnowski et al., supra). Preferably, the oligonucleotides are about 20 nucleotides in length.

cDNA probes labeled with an appropriate compound, such as biotin, digoxigenin or fluorescent dye, are

synthesized from the appropriate mRNA population and then randomly fragmented to an average size of 50 to 100 nucleotides. The said probes are then hybridized to the chip. After washing as described in Lockhart et al., supra and application of different electric fields (Sosnowsky et al., Proc. Natl. Acad. Sci. 94:1119-1123)., the dyes or labeling compounds are detected and quantified. Duplicate hybridizations are performed. Comparative analysis of the intensity of the signal originating from cDNA probes on the same target oligonucleotide in different cDNA samples indicates a differential expression of the mRNA corresponding to the 5' EST or extended cDNA from which the oligonucleotide sequence has been designed.

III. Use of 5' ESTs to Clone Extended cDNAs and to Clone the Corresponding Genomic DNAs

Once 5' ESTs which include the 5' end of the corresponding mRNAs have been selected using the procedures described above, they can be utilized to isolate extended cDNAs which contain sequences adjacent to the 5' ESTs. The extended cDNAs may include the entire coding sequence of the protein encoded by the corresponding mRNA, including the authentic translation start site, the signal sequence, and the sequence encoding the mature protein remaining after cleavage of the signal peptide. Such extended cDNAs are referred to herein as "full length cDNAs." Alternatively, the extended cDNAs may include only the sequence encoding the mature protein remaining after cleavage of the signal peptide, or only the sequence encoding the signal peptide.

Example 27 below describes a general method for obtaining extended cDNAs. Example 28 below describes the cloning and sequencing of several extended cDNAs, including extended cDNAs which include the entire coding sequence and authentic 5' end of the corresponding mRNA for several secreted proteins.

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The methods of Examples 27, 28, and 29 can also be used to obtain extended cDNAs which encode less than the entire coding sequence of the secreted proteins encoded by the genes corresponding to the 5' ESTs. In some embodiments, the extended cDNAs isolated using these methods encode at least 10 amino acids of one of the proteins encoded by the sequences of SEQ ID NOs: 40-140 and 242-377. In further embodiments, the extended cDNAs encode at least 20 amino acids of the proteins encoded by the sequences of SEQ ID NOs: 40-140 and 242-377. In further embodiments, the extended cDNAs encode at least 30 amino amino acids of the sequences of SEQ ID NOs: 40-140 and

242-377. In a preferred embodiment, the extended cDNAs encode a full length protein sequence, which includes the protein coding sequences of SEQ ID NOs: 40-140 and 242-377.

EXAMPLE 27

General Method for Using 5' ESTs to Clone and Sequence Extended cDNAs

The following general method has been used to quickly and efficiently isolate extended cDNAs including sequence adjacent to the sequences of the 5' ESTs used to obtain them. This method may be applied to obtain extended cDNAs for any 5' EST in the NETGENETM database, including those 5' ESTs encoding secreted proteins. The method is summarized in Figure 6.

1. Obtaining Extended cDNAs

10 a) First strand synthesis

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The method takes advantage of the known 5' sequence of the mRNA. A reverse transcription reaction is conducted on purified mRNA with a poly 14dT primer containing a 49 nucleotide sequence at its 5' end allowing the addition of a known sequence at the end of the cDNA which corresponds to the 3' end of the mRNA. For example, the primer may have the following sequence: 5'-ATC GTT GAG ACT CGT ACC AGC AGA GTC ACG AGA GAG ACT ACA CGG TAC TGG TTT TTT TTT TTT TTVN -3' (SEQ ID NO:14). Those skilled in the art will appreciate that other sequences may also be added to the poly dT sequence and used to prime the first strand synthesis. Using this primer and a reverse transcriptase such as the Superscript II (Gibco BRL) or Rnase H Minus M-MLV (Promega) enzyme, a reverse transcript anchored at the 3' polyA site of the RNAs is generated.

After removal of the mRNA hybridized to the first cDNA strand by alkaline hydrolysis, the products of the alkaline hydrolysis and the residual poly dT primer are eliminated with an exclusion column such as an AcA34 (Biosepra) matrix as explained in Example 11.

b) Second strand synthesis

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A pair of nested primers on each end is designed based on the known 5' sequence from the 5' EST and the known 3' end added by the poly dT primer used in the first strand synthesis. Software used to design primers are either based on GC content and melting temperatures of oligonucleotides, such as OSP (Illier and Green, *PCR Meth. Appl.* 1:124-128, 1991), or based on the octamer frequency disparity method (Griffais et al., *Nucleic Acids Res.* 19: 3887-3891, 1991 such as PC-Rare (http://bioinformatics.weizmann.ac.il/software/PC-Rare/doc/manuel.html).

Preferably, the nested primers at the 5' end are separated from one another by four to nine bases. The 5' primer sequences may be selected to have melting temperatures and specificities suitable for use in PCR.

Preferably, the nested primers at the 3' end are separated from one another by four to nine bases. For example, the nested 3' primers may have the following sequences: (5'- CCA GCA GAG TCA CGA GAG AGA CTA CAC GG -3'(SEQ ID NO:15), and 5'- CAC GAG AGA GAC TAC ACG GTA CTG G -3' (SEQ ID NO:16). These primers were selected because they have melting temperatures and specificities compatible with their use in PCR. However, those skilled in the art will appreciate that other sequences may also be used as primers.

The first PCR run of 25 cycles is performed using the Advantage Tth Polymerase Mix (Clontech) and the outer-primer from each of the nested pairs. A second 20 cycle PCR using the same enzyme and the inner primer from each of the nested pairs is then performed on 1/2500 of the first PCR product. Thereafter, the primers and nucleotides are removed.

5 2. Sequencing of Full Length Extended cDNAs or Fragments Thereof

Due to the lack of position constraints on the design of 5' nested primers compatible for PCR use using the OSP software, amplicons of two types are obtained. Preferably, the second 5' primer is located upstream of the translation initiation codon thus yielding a nested PCR product containing the whole coding sequence. Such a full length extended cDNA undergoes a direct cloning procedure as described in section a below. However, in some cases, the second 5' primer is located downstream of the translation initiation codon, thereby yielding a PCR product containing only part of the ORF. Such incomplete PCR products are submitted to a modified procedure described in section b below.

a) Nested PCR products containing complete ORFs

When the resulting nested PCR product contains the complete coding sequence, as predicted from the 5'EST sequence, it is cloned in an appropriate vector such as pED6dpc2, as described in section 3.

b) Nested PCR products containing incomplete ORFs

When the amplicon does not contain the complete coding sequence, intermediate steps are necessary to obtain both the complete coding sequence and a PCR product containing the full coding sequence. The complete coding sequence can be assembled from several partial sequences determined directly from different PCR products as described in the following section.

Once the full coding sequence has been completely determined, new primers compatible for PCR use are designed to obtain amplicons containing the whole coding region. However, in such cases, 3' primers compatible for PCR use are located inside the 3' UTR of the corresponding mRNA, thus yielding amplicons which lack part of this region, i.e. the polyA tract and sometimes the polyadenylation signal, as illustrated in figure 6. Such full length extended cDNAs are then cloned into an appropriate vector as described in section 3.

c) Sequencing extended cDNAs

Sequencing of extended cDNAs is performed using a Die Terminator approach with the AmpliTaq DNA polymerase FS kit available from Perkin Elmer.

In order to sequence PCR fragments, primer walking is performed using software such as OSP to choose

30 primers and automated computer software such as ASMG (Sutton et al., *Genome Science Technol.* 1: 9-19, 1995) to construct contigs of walking sequences including the initial 5' tag using minimum overlaps of 32 nucleotides. Preferably, primer walking is performed until the sequences of full length cDNAs are obtained.

Completion of the sequencing of a given extended cDNA fragment is assessed as follows. Since sequences located after a polyA tract are difficult to determine precisely in the case of uncloned products, sequencing and primer

walking processes for PCR products are interrupted when a polyA tract is identified in extended cDNAs obtained as described in case b. The sequence length is compared to the size of the nested PCR product obtained as described above. Due to the limited accuracy of the determination of the PCR product size by gel electrophoresis, a sequence is considered complete if the size of the obtained sequence is at least 70 % the size of the first nested PCR product. If the 5 length of the sequence determined from the computer analysis is not at least 70% of the length of the nested PCR product, these PCR products are cloned and the sequence of the insertion is determined. When Northern blot data are available, the size of the mRNA detected for a given PCR product is used to finally assess that the sequence is complete. Sequences which do not fulfill the above criteria are discarded and will undergo a new isolation procedure.

Sequence data of all extended cDNAs are then transferred to a proprietary database, where quality controls 10 and validation steps are carried out as described in example 15.

3. Cloning of Full Length Extended cDNAs

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The PCR product containing the full coding sequence is then cloned in an appropriate vector. For example, the extended cDNAs can be cloned into the expression vector pED6dpc2 (DiscoverEase, Genetics Institute, Cambridge, MA) as follows. The structure of pED6dpc2 is shown in Figure 7. pED6dpc2 vector DNA is prepared with blunt ends by 15 performing an EcoRI digestion followed by a fill in reaction. The blunt ended vector is dephosphorylated. After removal of PCR primers and ethanol precipitation, the PCR product containing the full coding sequence or the extended cDNA obtained as described above is phosphorylated with a kinase subsequently removed by phenol-Sevag extraction and precipitation. The double stranded extended cDNA is then ligated to the vector and the resulting expression plasmid introduced into appropriate host cells.

Since the PCR products obtained as described above are blunt ended molecules that can be cloned in either direction, the orientation of several clones for each PCR product is determined. Then, 4 to 10 clones are ordered in microtiter plates and subjected to a PCR reaction using a first primer located in the vector close to the cloning site and a second primer located in the portion of the extended cDNA corresponding to the 3' end of the mRNA. This second primer may be the antisense primer used in anchored PCR in the case of direct cloning (case a) or the antisense primer located 25 inside the 3'UTR in the case of indirect cloning (case b). Clones in which the start codon of the extended cDNA is operably linked to the promoter in the vector so as to permit expression of the protein encoded by the extended cDNA are conserved and sequenced. In addition to the ends of cDNA inserts, approximately 50 bp of vector DNA on each side of the cDNA insert are also sequenced.

The cloned PCR products are then entirely sequenced according to the aforementioned procedure. In this case, 30 contig assembly of long fragments is then performed on walking sequences that have already contigated for uncloned PCR products during primer walking. Sequencing of cloned amplicons is complete when the resulting contigs include the whole coding region as well as overlapping sequences with vector DNA on both ends.

4. Computer Analysis of Full Length Extended cDNA

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Sequences of all full length extended cDNAs are then submitted to further analysis as described below and using the parameters found in Table II with the following modifications. For screening of miscellaneous subdivisions of Genbank, FASTA was used instead of BLASTN and 15 nucleotide of homology was the limit instead of 17. For Alu detection, BLASTN was used with the following parameters: S = 72; identity = 70%; and length = 40 nucleotides.

- Polyadenylation signal and polyA tail which were not search for the 5' ESTs were searched. For polyadenylation signal detection the signal (AATAAA) was searched with one permissible mismatch in the last ten nucleotides preceding the 5' end of the polyA. For the polyA, a stretch of 8 amino acids in the last 20 nucleotides of the sequence was searched with BLAST2N in the sense strand with the following parameters (W = 6, S = 10, E = 1000, and identity = 90%). Finally, patented sequences and ORF homologies were searched using, respectively, BLASTN and BLASTP on GenSEQ (Derwent's database of patented nucleotide sequences) and SWISSPROT for ORFs with the following parameters (W = 8 and B = 10). Before examining the extended full length cDNAs for sequences of interest, extended cDNAs which are not
 - of interest are searched as follows.

 a) Elimination of undesired sequences

Although 5'ESTs were checked to remove contaminant sequences as described in Example 18, a last verification was carried out to identify extended cDNAs sequences derived from undesired sequences such as vector RNAs, transfer RNAs, ribosomal rRNAs, mitochondrial RNAs, prokaryotic RNAs and fungal RNAs using the FASTA and BLASTN programs on both strands of extended cDNAs as described below.

To identify the extended cDNAs encoding vector RNAs, extended cDNAs are compared to the known sequences of vector RNA using the FASTA program. Sequences of extended cDNAs with more than 90% homology over stretches of 15 nucleotides are identified as vector RNA.

To identify the extended cDNAs encoding tRNAs, extended cDNA sequences were compared to the sequences of 1190 known tRNAs obtained from EMBL release 38, of which 100 were human. Sequences of extended cDNAs having more than 80% homology over 60 nucleotides using FASTA were identified as tRNA.

To identify the extended cDNAs encoding rRNAs, extended cDNA sequences were compared to the sequences of 2497 known rRNAs obtained from EMBL release 38, of which 73 were human. Sequences of extended cDNAs having more than 80% homology over stretches longer than 40 nucleotides using BLASTN were identified as rRNAs.

To identify the extended cDNAs encoding mtRNAs, extended cDNA sequences were compared to the sequences of the two known mitochondrial genomes for which the entire genomic sequences are available and all sequences transcribed from these mitochondrial genomes including tRNAs, rRNAs, and mRNAs for a total of 38 sequences. Sequences of extended cDNAs having more than 80% homology over stretches longer than 40 nucleotides using BLASTN were identified as mtRNAs.

Sequences which might have resulted from other exogenous contaminants were identified by comparing extended cDNA sequences to release 105 of Genbank bacterial and fungal divisions. Sequences of extended cDNAs

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having more than 90% homology over 40 nucleotides using BLASTN were identified as exogenous prokaryotic or fungal contaminants.

In addition, extended cDNAs were searched for different repeat sequences, including Alu sequences, L1 sequences, THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats. Sequences of extended cDNAs with more than 70% homology over 40 nucleotide stretches using BLASTN were identified as repeat sequences and masked in further identification procedures. In addition, clones showing extensive homology to repeats, i.e., matches of either more than 50 nucleotides if the homology was at least 75% or more than 40 nucleotides if the homology was at least 90%, were flagged.

b) <u>Identification of structural features</u>

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Structural features, e.g. polyA tail and polyadenylation signal, of the sequences of full length extended cDNAs are subsequently determined as follows.

A polyA tail is defined as a homopolymeric stretch of at least 11 A with at most one alternative base within it.

The polyA tail search is restricted to the last 20 nt of the sequence and limited to stretches of 11 consecutive A's because sequencing reactions are often not readable after such a polyA stretch. Stretches with 100% homology over 6 nucleotides are identified as polyA tails.

To search for a polyadenylation signal, the polyA tail is clipped from the full-length sequence. The 50 bp preceding the polyA tail are searched for the canonic polyadenylation AAUAAA signal allowing one mismatch to account for possible sequencing errors and known variation in the canonical sequence of the polyadenylation signal.

c) Identification of functional features

Functional features, e.g. ORFs and signal sequences, of the sequences of full length extended cDNAs were subsequently determined as follows.

The 3 upper strand frames of extended cDNAs are searched for ORFs defined as the maximum length fragments beginning with a translation initiation codon and ending with a stop codon. ORFs encoding at least 20 amino acids are preferred.

Each found ORF is then scanned for the presence of a signal peptide in the first 50 amino-acids or, where appropriate, within shorter regions down to 20 amino acids or less in the ORF, using the matrix method of von Heijne (Nuc. Acids Res. 14: 4683-4690 (1986)) and the modification described in Example 22.

d) Homology to either nucleotidic or proteic sequences

Sequences of full length extended cDNAs are then compared to known sequences on a nucleotidic or proteic 30 basis.

Sequences of full length extended cDNAs are compared to the following known nucleic acid sequences: vertebrate sequences (Genbank), EST sequences (Genbank), patented sequences (Geneseqn) and recently identified sequences (Genbank daily releases) available at the time of filing for the priority documents. Full length cDNA sequences are also compared to the sequences of a private database (Genset internal sequences) in order to find sequences that

have already been identified by applicants. Sequences of full length extended cDNAs with more than 90% homology over 30 nucleotides using either BLASTN or BLAST2N as indicated in Table III are identified as sequences that have already been described. Matching vertebrate sequences are subsequently examined using FASTA; full length extended cDNAs with more than 70% homology over 30 nucleotides are identified as sequences that have already been described.

ORFs encoded by full length extended cDNAs as defined in section c) are subsequently compared to known amino acid sequences found in Swissprot release CHP, PIR release PIR# and Genpept release GPEPT public databases using BLASTP with the parameter W = 8 and allowing a maximum of 10 matches. Sequences of full length extended cDNAs showing extensive homology to known protein sequences are recognized as already identified proteins.

In addition, the three-frame conceptual translation products of the top strand of full length extended cDNAs are compared to publicly known amino acid sequences of Swissprot using BLASTX with the parameter E = 0.001. Sequences of full length extended cDNAs with more than 70% homology over 30 amino acid stretches are detected as already identified proteins.

5. Selection of Cloned Full Length Sequences of the Present Invention

Cloned full length extended cDNA sequences that have already been characterized by the aforementioned computer analysis are then submitted to an automatic procedure in order to preselect full length extended cDNAs containing sequences of interest.

a) Automatic sequence preselection

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All complete cloned full length extended cDNAs clipped for vector on both ends are considered. First, a negative selection is operated in order to eliminate unwanted cloned sequences resulting from either contaminants or PCR artifacts as follows. Sequences matching contaminant sequences such as vector RNA, tRNA, mtRNA, rRNA sequences are discarded as well as those encoding ORF sequences exhibiting extensive homology to repeats as defined in section 4 a). Sequences obtained by direct cloning using nested primers on 5' and 3' tags (section 1. case a) but lacking polyA tail are discarded. Only ORFs containing a signal peptide and ending either before the polyA tail (case a) or before the end of the cloned 3'UTR (case b) are kept. Then, ORFs containing unlikely mature proteins such as mature proteins which size is less than 20 amino acids or less than 25% of the immature protein size are eliminated.

In the selection of the OFR, priority was given to the ORF and the frame corresponding to the polypeptides described in SignalTag Patents (United States Patent Application Serial Nos: 08/905,223; 08/905,135; 08/905,051; 08/905,144; 08/905,279; 08/904,468; 08/905,134; and 08/905,133). If the ORF was not found among the OFRs described in the SignalTag Patents, the ORF encoding the signal peptide with the highest score according to Von Heijne method as defined in Example 22 was chosen. If the scores were identical, then the longest ORF was chosen.

Sequences of full length extended cDNA clones are then compared pairwise with BLAST after masking of the repeat sequences. Sequences containing at least 90% homology over 30 nucleotides are clustered in the same class. Each cluster is then subjected to a cluster analysis that detects sequences resulting from internal priming or from

alternative splicing, identical sequences or sequences with several frameshifts. This automatic analysis serves as a basis for manual selection of the sequences.

b) Manual sequence selection

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Manual selection is carried out using automatically generated reports for each sequenced full length extended cDNA clone. During this manual procedures, a selection is operated between clones belonging to the same class as follows. ORF sequences encoded by clones belonging to the same class are aligned and compared. If the homology between nucleotidic sequences of clones belonging to the same class is more than 90% over 30 nucleotide stretches or if the homology between amino acid sequences of clones belonging to the same class is more than 80% over 20 amino acid stretches, than the clones are considered as being identical. The chosen ORF is the best one according to the criteria mentioned below. If the nucleotide and amino acid homologies are less than 90% and 80% respectively, the clones are said to encode distinct proteins which can be both selected if they contain sequences of interest.

Selection of full length extended cDNA clones encoding sequences of interest is performed using the following criteria. Structural parameters (initial tag, polyadenylation site and signal) are first checked. Then, homologies with known nucleic acids and proteins are examined in order to determine whether the clone sequence match a known nucleic/proteic sequence and, in the latter case, its covering rate and the date at which the sequence became public. If there is no extensive match with sequences other than ESTs or genomic DNA, or if the clone sequence brings substantial new information, such as encoding a protein resulting from alternative slicing of an mRNA coding for an already known protein, the sequence is kept. Examples of such cloned full length extended cDNAs containing sequences of interest are described in Example 28. Sequences resulting from chimera or double inserts as assessed by homology to other sequences are discarded during this procedure.

EXAMPLE 28

Cloning and Sequencing of Extended cDNAs

The procedure described in Example 27 above was used to obtain the extended cDNAs of the present invention. Using this approach, the full length cDNA of SEQ ID NO:17 was obtained. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide MKKVLLLITAILAVAVG (SEQ ID NO: 18) having a von Heijne score of 8.2.

The full length cDNA of SEQ ID NO:19 was also obtained using this procedure. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide MWWFQQGLSFLPSALVIWTSA (SEQ ID NO:20) having a von Heijne score of 5.5.

Another full length cDNA obtained using the procedure described above has the sequence of SEQ ID NO:21.

This cDNA, falls into the "EST-ext" category described above and encodes the signal peptide

MVLTTLPSANSANSPVNMPTTGPNSLSYASSALSPCLT (SEQ ID NO:22) having a von Heijne score of 5.9.

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The above procedure was also used to obtain a full length cDNA having the sequence of SEQ ID NO:23. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide ILSTVTALTFAXA (SEQ ID NO:24) having a von Heijne score of 5.5.

The full length cDNA of SEQ ID NO:25 was also obtained using this procedure. This cDNA falls into the "new" category described above and encodes a signal peptide LVLTLCTLPLAVA (SEQ ID NO:26) having a von Heijne score of 10.1.

The full length cDNA of SEQ ID NO:27 was also obtained using this procedure. This cDNA falls into the "new" category described above and encodes a signal peptide LWLLFFLVTAIHA (SEQ ID NO:28) having a von Heijne score of 10.7.

The above procedures were also used to obtain the extended cDNAs of the present invention. 5' ESTs expressed in a variety of tissues were obtained as described above. The appended sequence listing provides the tissues from which the extended cDNAs were obtained. It will be appreciated that the extended cDNAs may also be expressed in tissues other than the tissue listed in the sequence listing.

5' ESTs obtained as described above were used to obtain extended cDNAs having the sequences of SEQ ID NOs: 40-140 and 242-377. Table IV provides the sequence identification numbers of the extended cDNAs of the present invention, the locations of the full coding sequences in SEQ ID NOs: 40-140 and 242-377 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the signal peptides (listed under the heading SigPep Location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of stop codons (listed under the heading Stop Codon Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of polyA signals (listed under the heading Poly A Signal Location in Table IV) and the locations of polyA sites (listed under the heading Poly A Site Location in Table IV).

The polypeptides encoded by the extended cDNAs were screened for the presence of known structural or functional motifs or for the presence of signatures, small amino acid sequences which are well conserved amongst the members of a protein family. The conserved regions have been used to derive consensus patterns or matrices included in the PROSITE data bank, in particular in the file prosite.dat (Release 13.0 of November 1995, located at http://expasy.hcuge.ch/sprot/prosite.html. Prosite_convert and prosite_scan programs (http://ulrec3.unil.ch/ftpserveur/prosite scan) were used to find signatures on the extended cDNAs.

For each pattern obtained with the prosite_convert program from the prosite.dat file, the accuracy of the detection on a new protein sequence has been tested by evaluating the frequency of irrelevant hits on the population of human secreted proteins included in the data bank SWISSPROT. The ratio between the number of hits on shuffled proteins (with a window size of 20 amino acids) and the number of hits on native (unshuffled) proteins was used as an index. Every pattern for which the ration was greater than 20% (one hit on shuffled proteins for 5 hits on native

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proteins) was skipped during the search with prosite_scan. The program used to shuffle protein sequences (db_shuffled) and the program used to determine the statistics for each pattern in the protein data banks (prosite statistics) are available on the ftp site http://ulrec3.unil.ch/ftpserveur/prosite scan.

Table V lists the sequence identification numbers of the polypeptides of SEQ ID NOs: 141-241 and 378-513, the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the full length polypeptide (second column), the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the signal peptides (third column), and the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the mature polypeptide created by cleaving the signal peptide from the full length polypeptide (fourth column).

The nucleotide sequences of the sequences of SEQ ID NOs: 40-140 and 242-377 and the amino acid sequences encoded by SEQ ID NOs: 40-140 and 242-377 (i.e. amino acid sequences of SEQ ID NOs: 141-241 and 378-513) are provided in the appended sequence listing. In some instances, the sequences are preliminary and may include some incorrect or ambiguous sequences or amino acids. The sequences of SEQ ID NOs: 40-140 and 242-377 can readily be screened for any errors therein and any sequence ambiguities can be resolved by resequencing a fragment containing such errors or ambiguities on both strands. Nucleic acid fragments for resolving sequencing errors or ambiguities may be obtained from the deposited clones or can be isolated using the techniques described herein. Resolution of any such ambiguities or errors may be facilitated by using primers which hybridize to sequences located close to the ambiguous or erroneous sequences. For example, the primers may hybridize to sequences within 50-75 bases of the ambiguity or error. Upon resolution of an error or ambiguity, the corresponding corrections can be made in the protein sequences encoded by the DNA containing the error or ambiguity. For example, in the sequences of the present invention, ambiguities in the sequence of SEQ ID NO: 131 were resolved. The amino acid sequence of the protein encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein, and determining its sequence.

For each amino acid sequence, Applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing. Some of the amino acid sequences may contain "Xaa" designators. These "Xaa" designators indicate either (1) a residue which cannot be identified because of nucleotide sequence ambiguity or (2) a stop codon in the determined sequence where Applicants believe one should not exist (if the sequence were determined more accurately).

Cells containing the extended cDNAs (SEQ ID NOs: 40-140 and 242-377) of the present invention in the vector pED6dpc2, are maintained in permanent deposit by the inventors at Genset, S.A., 24 Rue Royale, 75008 Paris, France.

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Pools of cells containing the extended cDNAs (SEQ ID NOs: 40-140 and 242-377), from which cells containing a particular polynucleotide are obtainable, were deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209 or the European Collection of Cell Cultures, Vaccine Research and Production Laboratory, Public Health Laboratory Service, Centre for Applied Microbiology and Research, Porton Down, Salisbury, Wiltshire SP4 0JG, United Kingdom. Each extended cDNA clone has been transfected into separate bacterial cells (E-

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coli) for this composite deposit. Table VI lists the deposit numbers of the clones containing the extended cDNAs of the present invention. Table VII provides the internal designation number assigned to each SEQ ID NO and indicates whether the sequence is a nucleic acid sequence or a protein sequence.

Each extended cDNA can be removed from the pED6dpc2 vector in which it was deposited by performing a 5 Notl, Pstl double digestion to produce the appropriate fragment for each clone. The proteins encoded by the extended cDNAs may also be expressed from the promoter in pED6dpc2.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The design 10 of the oligonucleotide probe should preferably follow these parameters:

(a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;

(b) Preferably, the probe is designed to have a T_m of approx. 80°C (assuming 2 degrees for each A or T and 4 degrees for each G or C). However, probes having melting temperatures between 40 °C and 80 °C may also be used provided that specificity is not lost.

The oligonucleotide should preferably be labeled with (-[32P]ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantified by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4X108 dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 μl of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 ug/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing 25 ampicillin at 100 μg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 30 175.3 g NaC1/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 pg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1X106 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to

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1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

The plasmid DNA obtained using these procedures may then be manipulated using standard cloning techniques familiar to those skilled in the art. Alternatively, a PCR can be done with primers designed at both ends of the extended cDNA insertion. For example, a PCR reaction may be conducted using a primer having the sequence GGCCATACACTTGAGTGAC (SEQ ID NO:38) and a primer having the sequence ATATAGACAAACGCACACC (SEQ. ID. NO:39). The PCR product which corresponds to the extended cDNA can then be manipulated using standard cloning 10 techniques familiar to those skilled in the art.

In addition to PCR based methods for obtaining extended cDNAs, traditional hybridization based methods may also be employed. These methods may also be used to obtain the genomic DNAs which encode the mRNAs from which the 5' ESTs were derived, mRNAs corresponding to the extended cDNAs, or nucleic acids which are homologous to extended cDNAs or 5' ESTs. Example 29 below provides an example of such methods.

15 **EXAMPLE 29**

Methods for Obtaining Extended cDNAs or Nucleic Acids Homologous to Extended cDNAs or 5' ESTs

A full length cDNA library can be made using the strategies described in Examples 13, 14, 15, and 16 above by replacing the random nonamer used in Example 14 with an oligo-dT primer. For instance, the oligonucleotide of SEQ ID 20 NO:14 may be used.

Alternatively, a cDNA library or genomic DNA library may be obtained from a commercial source or made using techniques familiar to those skilled in the art. The library includes cDNAs which are derived from the mRNA corresponding to a 5' EST or which have homology to an extended cDNA or 5' EST. The cDNA library or genomic DNA library is hybridized to a detectable probe comprising at least 10 consecutive nucleotides from the 5' EST or extended 25 cDNA using conventional techniques. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST or extended cDNA. More preferably, the probe comprises at least 20-30 consecutive nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises at least 30 nucleotides from the 5' EST or extended cDNA. In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST or extended cDNA.

Techniques for identifying cDNA clones in a cDNA library which hybridize to a given probe seguence are disclosed in Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold Spring Harbor Laboratory Press, 1989. The same techniques may be used to isolate genomic DNAs.

Briefly, cDNA or genomic DNA clones which hybridize to the detectable probe are identified and isolated for further manipulation as follows. A probe comprising at least 10 consecutive nucleotides from the 5' EST or extended cDNA is labeled with a detectable label such as a radioisotope or a fluorescent molecule. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST or extended cDNA. More preferably, the probe comprises 20-30 consecutive nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises more than 30 nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST or extended cDNA.

Techniques for labeling the probe are well known and include phosphorylation with polynucleotide kinase, nick translation, in vitro transcription, and non-radioactive techniques. The cDNAs or genomic DNAs in the library are transferred to a nitrocellulose or nylon filter and denatured. After incubation of the filter with a blocking solution, the filter is contacted with the labeled probe and incubated for a sufficient amount of time for the probe to hybridize to cDNAs or genomic DNAs containing a sequence capable of hybridizing to the probe.

By varying the stringency of the hybridization conditions used to identify extended cDNAs or genomic DNAs which hybridize to the detectable probe, extended cDNAS having different levels of homology to the probe can be identified and isolated. To identify extended cDNAs or genomic DNAs having a high degree of homology to the probe sequence, the melting temperature of the probe may be calculated using the following formulas:

For probes between 14 and 70 nucleotides in length the melting temperature (Tm) is calculated using the formula: Tm = 81.5 + 16.6(log [Na +]) + 0.41(fraction G + C)-(600/N) where N is the length of the probe.

If the hybridization is carried out in a solution containing formamide, the melting temperature may be calculated using the equation Tm = 81.5 + 16.6(log [Na+]) + 0.41(fraction G+C) - (0.63% formamide) - (600/N) where N is the length of the probe.

Prehybridization may be carried out in 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100µg denatured fragmented salmon sperm DNA or 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100µg denatured fragmented salmon sperm DNA, 50% formamide. The formulas for SSC and Denhardt's solutions are listed in Sambrook et al., supra.

Hybridization is conducted by adding the detectable probe to the prehybridization solutions listed above. Where the probe comprises double stranded DNA, it is denatured before addition to the hybridization solution. The filter is contacted with the hybridization solution for a sufficient period of time to allow the probe to hybridize to extended cDNAs or genomic DNAs containing sequences complementary thereto or homologous thereto. For probes over 200 nucleotides in length, the hybridization may be carried out at 15-25°C below the Tm. For shorter probes, such as oligonucleotide probes, the hybridization may be conducted at 15-25°C below the Tm. Preferably, for hybridizations in 6X SSC, the hybridization is conducted at approximately 68°C. Preferably, for hybridizations in 50% formamide containing solutions, the hybridization is conducted at approximately 42°C.

All of the foregoing hybridizations would be considered to be under "stringent" conditions. Following hybridization, the filter is washed in 2X SSC, 0.1% SDS at room temperature for 15 minutes. The filter is then washed

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with 0.1X SSC, 0.5% SDS at room temperature for 30 minutes to 1 hour. Thereafter, the solution is washed at the hybridization temperature in 0.1X SSC, 0.5% SDS. A final wash is conducted in 0.1X SSC at room temperature.

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Extended cDNAs, nucleic acids homologous to extended cDNAs or 5' ESTs, or genomic DNAs which have hybridized to the probe are identified by autoradiography or other conventional techniques.

The above procedure may be modified to identify extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs having decreasing levels of homology to the probe sequence. For example, to obtain extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs of decreasing homology to the detectable probe, less stringent conditions may be used. For example, the hybridization temperature may be decreased in increments of 5°C from 68°C to 42°C in a hybridization buffer having a Na+ concentration of approximately 1M. Following 10 hybridization, the filter may be washed with 2X SSC, 0.5% SDS at the temperature of hybridization. These conditions are considered to be "moderate" conditions above 50°C and "low" conditions below 50°C.

Alternatively, the hybridization may be carried out in buffers, such as 6X SSC, containing formamide at a temperature of 42°C. In this case, the concentration of formamide in the hybridization buffer may be reduced in 5% increments from 50% to 0% to identify clones having decreasing levels of homology to the probe. Following 15 hybridization, the filter may be washed with 6X SSC, 0.5% SDS at 50°C. These conditions are considered to be "moderate" conditions above 25% formamide and "low" conditions below 25% formamide.

Extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs which have hybridized to the probe are identified by autoradiography.

If it is desired to obtain nucleic acids homologous to extended cDNAs, such as allelic variants thereof or nucleic 20 acids encoding proteins related to the proteins encoded by the extended cDNAs, the level of homology between the hybridized nucleic acid and the extended cDNA or 5' EST used as the probe may readily be determined. To determine the level of homology between the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived, the nucleotide sequences of the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived are compared. For example, using the above methods, nucleic acids having at least 95% nucleic acid 25 homology to the extended cDNA or 5'EST from which the probe was derived may be obtained and identified. Similarly, by using progressively less stringent hybridization conditions one can obtain and identify nucleic acids having at least 90%, at least 85%, at least 80% or at least 75% homology to the extended cDNA or 5'EST from which the probe was derived. The level of homology between the hybridized nucleic acid and the extended cDNA or 5' EST used as the probe may be further determined using BLAST2N; parameters may be adapted depending on the sequence length and degree of 30 homology studied. In such comparisons, the default parameters or the parameters listed in Tables II and III may be used.

To determine whether a clone encodes a protein having a given amount of homology to the protein encoded by the extended cDNA or 5' EST, the amino acid sequence encoded by the extended cDNA or 5' EST is compared to the amino acid sequence encoded by the hybridizing nucleic acid. Homology is determined to exist when an amino acid sequence in the extended cDNA or 5' EST is closely related to an amino acid sequence in the hybridizing nucleic acid. A

sequence is closely related when it is identical to that of the extended cDNA or 5' EST or when it contains one or more amino acid substitutions therein in which amino acids having similar characteristics have been substituted for one another. Using the above methods, one can obtain nucleic acids encoding proteins having at least 95%, at least 90%, at least 85%, at least 80% or at least 75% homology to the proteins encoded by the extended cDNA or 5'EST from which the probe was derived. Using the above methods and algorithms such as FASTA with parameters depending on the sequence length and degree of homology studied the level of homology may be determined. In determining the level of

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Alternatively, extended cDNAs may be prepared by obtaining mRNA from the tissue, cell, or organism of interest using mRNA preparation procedures utilizing poly A selection procedures or other techniques known to those skilled in the art. A first primer capable of hybridizing to the poly A tail of the mRNA is hybridized to the mRNA and a reverse transcription reaction is performed to generate a first cDNA strand.

homology using FASTA, the default parameters or the parameters listed in Tables II or III may be used.

The first cDNA strand is hybridized to a second primer containing at least 10 consecutive nucleotides of the sequences of the 5' EST for which an extended cDNA is desired. Preferably, the primer comprises at least 12, 15, or 17 consecutive nucleotides from the sequences of the 5' EST. More preferably, the primer comprises 20-30 consecutive nucleotides from the sequences of the 5' EST. In some embodiments, the primer comprises more than 30 nucleotides from the sequences of the 5' EST. If it is desired to obtain extended cDNAs containing the full protein coding sequence, including the authentic translation initiation site, the second primer used contains sequences located upstream of the translation initiation site. The second primer is extended to generate a second cDNA strand complementary to the first cDNA strand. Alternatively, RTPCR may be performed as described above using primers from both ends of the cDNA to be obtained.

Extended cDNAs containing 5' fragments of the mRNA may be prepared by contacting an mRNA comprising the sequence of the 5' EST for which an extended cDNA is desired with a primer comprising at least 10 consecutive nucleotides of the sequences complementary to the 5' EST, hybridizing the primer to the mRNAs, and reverse transcribing the hybridized primer to make a first cDNA strand from the mRNAs. Preferably, the primer comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST. More preferably, the primer comprises 20-30 consecutive nucleotides from the 5' EST.

Thereafter, a second cDNA strand complementary to the first cDNA strand is synthesized. The second cDNA strand may be made by hybridizing a primer complementary to sequences in the first cDNA strand to the first cDNA strand and extending the primer to generate the second cDNA strand.

The double stranded extended cDNAs made using the methods described above are isolated and cloned. The extended cDNAs may be cloned into vectors such as plasmids or viral vectors capable of replicating in an appropriate host cell. For example, the host cell may be a bacterial, mammalian, avian, or insect cell.

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Techniques for isolating mRNA, reverse transcribing a primer hybridized to mRNA to generate a first cDNA strand, extending a primer to make a second cDNA strand complementary to the first cDNA strand, isolating the double

stranded cDNA and cloning the double stranded cDNA are well known to those skilled in the art and are described in Current Protocols in Molecular Biology, John Wiley 503 Sons, Inc. 1997 and Sambrook et al. Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989.

Alternatively, kits for obtaining full length cDNAs, such as the GeneTrapper (Cat. No. 10356-020, Gibco, BRL),

may be used for obtaining full length cDNAs or extended cDNAs. In this approach, full length or extended cDNAs are
prepared from mRNA and cloned into double stranded phagemids. The cDNA library in the double stranded phagemids is
then rendered single stranded by treatment with an endonuclease, such as the Gene II product of the phage F1, and
Exonuclease III as described in the manual accompanying the GeneTrapper kit. A biotinylated oligonucleotide comprising
the sequence of a 5' EST, or a fragment containing at least 10 nucleotides thereof, is hybridized to the single stranded
phagemids. Preferably, the fragment comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST. More
preferably, the fragment comprises 20-30 consecutive nucleotides from the 5' EST. In some procedures, the fragment
may comprise more than 30 consecutive nucleotides from the 5' EST. For example, the fragment may comprises at least
40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST.

Hybrids between the biotinylated oligonucleotide and phagemids having inserts containing the 5' EST sequence are isolated by incubating the hybrids with streptavidin coated paramagnetic beads and retrieving the beads with a magnet. Thereafter, the resulting phagemids containing the 5' EST sequence are released from the beads and converted into double stranded DNA using a primer specific for the 5' EST sequence. The resulting double stranded DNA is transformed into bacteria. Extended cDNAs containing the 5' EST sequence are identified by colony PCR or colony hybridization.

A plurality of extended cDNAs containing full length protein coding sequences or sequences encoding only the mature protein remaining after the signal peptide is cleaved may be provided as cDNA libraries for subsequent evaluation of the encoded proteins or use in diagnostic assays as described below.

IV. Expression of Proteins Encoded by Extended cDNAs Isolated Using 5' ESTs

Extended cDNAs containing the full protein coding sequences of their corresponding mRNAs or portions

thereof, such as cDNAs encoding the mature protein, may be used to express the secreted proteins or portions thereof which they encode as described in Example 30 below. If desired, the extended cDNAs may contain the sequences encoding the signal peptide to facilitate secretion of the expressed protein. It will be appreciated that a plurality of extended cDNAs containing the full protein coding sequences or portions thereof may be simultaneously cloned into expression vectors to create an expression library for analysis of the encoded proteins as described below.

30 EXAMPLE 30

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Expression of the Proteins Encoded by Extended cDNAs or Portions Thereof

To express the proteins encoded by the extended cDNAs or portions thereof, nucleic acids containing the coding sequence for the proteins or portions thereof to be expressed are obtained as described in Examples 27-29 and cloned into a suitable expression vector. If desired, the nucleic acids may contain the sequences encoding the signal

peptide to facilitate secretion of the expressed protein. For example, the nucleic acid may comprise the sequence of one of SEQ ID NOs: 40-140 and 242-377 listed in Table IV and in the accompanying sequence listing. Alternatively, the nucleic acid may comprise those nucleotides which make up the full coding sequence of one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

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15 It will be appreciated that should the extent of the full coding sequence (i.e. the sequence encoding the signal peptide and the mature protein resulting from cleavage of the signal peptide) differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the full coding sequences in the sequences of SEQ ID NOs. 40-140 and 242-377.

10 For example, the sequence of SEQ ID NO: 115 represents an alternatively spliced transcript of a previously identified mRNA.. Accordingly, the scope of any claims herein relating to nucleic acids containing the full coding sequence of one of SEQ ID NOs. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from or equivalents to the full coding sequences listed in Table IV Similarly, should the extent of the full length polypeptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the amino acid sequence of the full length polypeptides is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table V.

Alternatively, the nucleic acid used to express the protein or portion thereof may comprise those nucleotides which encode the mature protein (i.e. the protein created by cleaving the signal peptide off) encoded by one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

20 It will be appreciated that should the extent of the sequence encoding the mature protein differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, posttranslational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the mature protein in the sequences of SEQ ID NOs. 40-140 and 242-377. Accordingly, the scope of any claims herein relating to nucleic acids 25 containing the sequence encoding the mature protein encoded by one of SEQ ID Nos. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table IV. Thus, claims relating to nucleic acids containing the sequence encoding the mature protein encompass equivalents to the sequences listed in Table IV, such as sequences encoding biologically active proteins resulting from post-translational modification, enzymatic cleavage, or other readily identifiable variations from or equivalents to the secreted proteins in 30 addition to cleavage of the signal peptide. Similarly, should the extent of the mature polypeptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a mature protein included in the sequence of one of SEQ ID NOs. 141-241 and 378-513 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table V. Thus, claims relating to polypeptides comprising the sequence of the mature protein encompass equivalents to the sequences

listed in Table IV, such as biologically active proteins resulting from post-translational modification, enzymatic cleavage, or other readily identifiable variations from or equivalents to the secreted proteins in addition to cleavage of the signal peptide. It will also be appreciated that should the biologically active form of the polypeptides included in the sequence of one of SEQ ID NOs. 141-241 and 378-513 or the nucleic acids encoding the biologically active form of the polypeptides differ from those identified as the mature polypeptide in Table V or the nucleotides encoding the mature polypeptide in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the amino acids in the biologically active form of the polypeptides and the nucleic acids encoding the biologically active form of the polypeptides. In such instances, the claims relating to polypetides comprising the mature protein included in one of SEQ ID NOs. 141-241 and 378-513 or nucleic acids comprising the nucleotides of one of SEQ ID NOs. 40-140 and 242-377 encoding the mature protein shall not be construed to exclude any readily identifiable variations from the sequences listed in Table IV and Table V.

In some embodiments, the nucleic acid used to express the protein or portion thereof may comprise those nucleotides which encode the signal peptide encoded by one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

It will be appreciated that should the extent of the sequence encoding the signal peptide differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the signal peptide in the sequences of SEQ ID Nos. 40-140 and 242-377. Accordingly, the scope of any claims herein relating to nucleic acids containing the sequence encoding the signal peptide encoded by one of SEQ ID Nos. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from the sequences listed in Table IV. Similarly, should the extent of the signal peptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a signal peptide included in the sequence of one of SEQ ID Nos. 141-241 and 378-513 is not to be construed as excluding any readily identifiable variations from the sequences listed in Table V.

Alternatively, the nucleic acid may encode a polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEO ID NOs: 141-241 and 378-513. In some embodiments, the nucleic acid may encode a polypeptide comprising at least 15 consecutive amino acids of one of the sequences of SEO ID NOs: 141-241 and 378-30 513. In other embodiments, the nucleic acid may encode a polypeptide comprising at least 25 consecutive amino acids of one of the sequences of SEO ID NOs: 141-241 and 378-513. In other embodiments, the nucleic acid may encode a polypeptide comprising at least 60, at least 75, at least 100 or more than 100 consecutive amino acids of one of the sequences of SEO ID Nos: 141-241 and 378-513.

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The nucleic acids inserted into the expression vectors may also contain sequences upstream of the sequences encoding the signal peptide, such as sequences which regulate expression levels or sequences which confer tissue specific expression.

The nucleic acid encoding the protein or polypeptide to be expressed is operably linked to a promoter in an 5 expression vector using conventional cloning technology. The expression vector may be any of the mammalian, yeast, insect or bacterial expression systems known in the art. Commercially available vectors and expression systems are available from a variety of suppliers including Genetics Institute (Cambridge, MA), Stratagene (La Jolla, California), Promega (Madison, Wisconsin), and Invitrogen (San Diego, California). If desired, to enhance expression and facilitate proper protein folding, the codon context and codon pairing of the sequence may be optimized for the particular 10 expression organism in which the expression vector is introduced, as explained by Hatfield, et al., U.S. Patent No. 5,082,767.

The following is provided as one exemplary method to express the proteins encoded by the extended cDNAs corresponding to the 5' ESTs or the nucleic acids described above. First, the methionine initiation codon for the gene and the poly A signal of the gene are identified. If the nucleic acid encoding the polypeptide to be expressed lacks a 15 methionine to serve as the initiation site, an initiating methionine can be introduced next to the first codon of the nucleic acid using conventional techniques. Similarly, if the extended cDNA lacks a poly A signal, this sequence can be added to the construct by, for example, splicing out the Poly A signal from pSG5 (Stratagene) using Bgll and Sall restriction endonuclease enzymes and incorporating it into the mammalian expression vector pXT1 (Stratagene). pXT1 contains the LTRs and a portion of the gag gene from Moloney Murine Leukemia Virus. The position of the LTRs in the construct 20 allow efficient stable transfection. The vector includes the Herpes Simplex Thymidine Kinase promoter and the selectable neomycin gene. The extended cDNA or portion thereof encoding the polypeptide to be expressed is obtained by PCR from the bacterial vector using oligonucleotide primers complementary to the extended cDNA or portion thereof and containing restriction endonuclease sequences for Pst I incorporated into the 5' primer and BgIII at the 5' end of the corresponding cDNA 3' primer, taking care to ensure that the extended cDNA is positioned in frame with the poly A 25 signal. The purified fragment obtained from the resulting PCR reaction is digested with Pstl, blunt ended with an exonuclease, digested with Bgl II, purified and ligated to pXT1, now containing a poly A signal and digested with BglII.

The ligated product is transfected into mouse NIH 3T3 cells using Lipofectin (Life Technologies, Inc., Grand Island, New York) under conditions outlined in the product specification. Positive transfectants are selected after growing the transfected cells in 600ug/ml G418 (Sigma, St. Louis, Missouri). Preferably the expressed protein is 30 released into the culture medium, thereby facilitating purification.

Alternatively, the extended cDNAs may be cloned into pED6dpc2 as described above. The resulting pED6dpc2 constructs may be transfected into a suitable host cell, such as COS 1 cells. Methotrexate resistant cells are selected and expanded. Preferably, the protein expressed from the extended cDNA is released into the culture medium thereby facilitating purification.

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Proteins in the culture medium are separated by gel electrophoresis. If desired, the proteins may be ammonium sulfate precipitated or separated based on size or charge prior to electrophoresis.

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As a control, the expression vector lacking a cDNA insert is introduced into host cells or organisms and the proteins in the medium are harvested. The secreted proteins present in the medium are detected using techniques such as Coomassie or silver staining or using antibodies against the protein encoded by the extended cDNA. Coomassie and silver staining techniques are familiar to those skilled in the art.

Antibodies capable of specifically recognizing the protein of interest may be generated using synthetic 15-mer peptides having a sequence encoded by the appropriate 5' EST, extended cDNA, or portion thereof. The synthetic peptides are injected into mice to generate antibody to the polypeptide encoded by the 5' EST, extended cDNA, or portion thereof.

Secreted proteins from the host cells or organisms containing an expression vector which contains the extended cDNA derived from a 5' EST or a portion thereof are compared to those from the control cells or organism. The presence of a band in the medium from the cells containing the expression vector which is absent in the medium from the control cells indicates that the extended cDNA encodes a secreted protein. Generally, the band corresponding to the protein encoded by the extended cDNA will have a mobility near that expected based on the number of amino acids in the open reading frame of the extended cDNA. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

Alternatively, if the protein expressed from the above expression vectors does not contain sequences directing its secretion, the proteins expressed from host cells containing an expression vector containing an insert encoding a secreted protein or portion thereof can be compared to the proteins expressed in host cells containing the expression vector without an insert. The presence of a band in samples from cells containing the expression vector with an insert which is absent in samples from cells containing the expression vector without an insert indicates that the desired protein or portion thereof is being expressed. Generally, the band will have the mobility expected for the secreted protein or portion thereof. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

The protein encoded by the extended cDNA may be purified using standard immunochromatography techniques. In such procedures, a solution containing the secreted protein, such as the culture medium or a cell extract, is applied to a column having antibodies against the secreted protein attached to the chromatography matrix. The secreted protein is allowed to bind the immunochromatography column. Thereafter, the column is washed to remove non-specifically bound proteins. The specifically bound secreted protein is then released from the column and recovered using standard techniques.

If antibody production is not possible, the extended cDNA sequence or portion thereof may be incorporated into expression vectors designed for use in purification schemes employing chimeric polypeptides. In such strategies the coding sequence of the extended cDNA or portion thereof is inserted in frame with the gene encoding the other half of

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the chimera. The other half of the chimera may be β-globin or a nickel binding polypeptide encoding sequence. A chromatography matrix having antibody to β-globin or nickel attached thereto is then used to purify the chimeric protein. Protease cleavage sites may be engineered between the β-globin gene or the nickel binding polypeptide and the extended cDNA or portion thereof. Thus, the two polypeptides of the chimera may be separated from one another by protease digestion.

One useful expression vector for generating β-globin chimerics is pSG5 (Stratagene), which encodes rabbit β-globin. Intron II of the rabbit β-globin gene facilitates splicing of the expressed transcript, and the polyadenylation signal incorporated into the construct increases the level of expression. These techniques as described are well known to those skilled in the art of molecular biology. Standard methods are published in methods texts such as Davis et al.,

10 (Basic Methods in Molecular Biology, L.G. Davis, M.D. Dibner, and J.F. Battey, ed., Elsevier Press, NY, 1986) and many of the methods are available from Stratagene, Life Technologies, Inc., or Promega. Polypeptide may additionally be produced from the construct using in vitro translation systems such as the In vitro ExpressTM Translation Kit (Stratagene).

Following expression and purification of the secreted proteins encoded by the 5' ESTs, extended cDNAs, or fragments thereof, the purified proteins may be tested for the ability to bind to the surface of various cell types as described in Example 31 below. It will be appreciated that a plurality of proteins expressed from these cDNAs may be included in a panel of proteins to be simultaneously evaluated for the activities specifically described below, as well as other biological roles for which assays for determining activity are available.

EXAMPLE 31

20 Analysis of Secreted Proteins to Determine Whether they Bind to the Cell Surface

The proteins encoded by the 5' ESTs, extended cDNAs, or fragments thereof are cloned into expression vectors such as those described in Example 30. The proteins are purified by size, charge, immunochromatography or other techniques familiar to those skilled in the art. Following purification, the proteins are labeled using techniques known to those skilled in the art. The labeled proteins are incubated with cells or cell lines derived from a variety of organs or tissues to allow the proteins to bind to any receptor present on the cell surface. Following the incubation, the cells are washed to remove non-specifically bound protein. The labeled proteins are detected by autoradiography. Alternatively, unlabeled proteins may be incubated with the cells and detected with antibodies having a detectable label, such as a fluorescent molecule, attached thereto.

Specificity of cell surface binding may be analyzed by conducting a competition analysis in which various

amounts of unlabeled protein are incubated along with the labeled protein. The amount of labeled protein bound to the

cell surface decreases as the amount of competitive unlabeled protein increases. As a control, various amounts of an

unlabeled protein unrelated to the labeled protein is included in some binding reactions. The amount of labeled protein

bound to the cell surface does not decrease in binding reactions containing increasing amounts of unrelated unlabeled

protein, indicating that the protein encoded by the cDNA binds specifically to the cell surface.

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As discussed above, secreted proteins have been shown to have a number of important physiological effects and, consequently, represent a valuable therapeutic resource. The secreted proteins encoded by the extended cDNAs or portions thereof made according to Examples 27-29 may be evaluated to determine their physiological activities as described below.

5 EXAMPLE 32

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Cytokine, Cell Proliferation or Cell Differentiation Activity

As discussed above, secreted proteins may act as cytokines or may affect cellular proliferation or differentiation. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B5, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7c and CMK. The proteins encoded by the above extended cDNAs or portions thereof may be evaluated for their ability to regulate T cell or thymocyte proliferation in assays such as those described above or in the following references: Current Protocols in Immunology, Ed. by J.E. Coligan et al., Greene Publishing Associates and Wiley-Interscience; Takai et al. J. Immunol. 137:3494-3500, 1986. Bertagnolli et al. J. Immunol. 145:1706-1712, 1990. Bertagnolli et al., Cellular Immunology 133:327-341, 1991. Bertagnolli, et al. J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152:1756-1761, 1994.

In addition, numerous assays for cytokine production and/or the proliferation of spleen cells, lymph node cells
and thymocytes are known. These include the techniques disclosed in Current Protocols in Immunology. J.E. Coligan
et al. Eds., Vol 1 pp. 3.12.1-3.12.14 John Wiley and Sons, Toronto. 1994; and Schreiber, R.D. Current Protocols in
Immunology., supra Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be assayed for the ability to regulate the proliferation and differentiation of hematopoietic or lymphopoietic cells. Many assays for such activity are familiar to those skilled in the art, including the assays in the following references: Bottomly, K., Davis, L.S. and Lipsky, P.E., Measurement of Human and Murine Interleukin 2 and Interleukin 4, Current Protocols in Immunology., J.E. Coligan et al. Eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 36:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Nordan, R., Measurement of Mouse and Human Interleukin 6 Current Protocols in Immunology. J.E. Coligan et al. Eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Bennett, F., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Human Interleukin 11 Current Protocols in Immunology. J.E. Coligan et al. Eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Mouse and Human Interleukin 9 Current Protocols in Immunology. J.E. Coligan et al., Eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

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The proteins encoded by the cDNAs may also be assayed for their ability to regulate T-cell responses to antigens. Many assays for such activity are familiar to those skilled in the art, including the assays described in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function), Chapter 6 (Cytokines and Their Cellular Receptors) and Chapter 7, (Immunologic Studies in Humans) in Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience; Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Those proteins which exhibit cytokine, cell proliferation, or cell differentiation activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which induction of cell proliferation or differentiation is beneficial. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 33

Assaying the Proteins Expressed from Extended cDNAs or Portions

Thereof for Activity as Immune System Regulators

The proteins encoded by the cDNAs may also be evaluated for their effects as immune regulators. For example, the proteins may be evaluated for their activity to influence thymocyte or splenocyte cytotoxicity. Numerous assays for such activity are familiar to those skilled in the art including the assays described in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function 3.1-3.19) and Chapter 7 (Immunologic studies in Humans) in 20 Current Protocols in Immunology, J.E. Coligan et al. Eds, Greene Publishing Associates and Wiley-Interscience; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowman et al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

The proteins encoded by the cDNAs may also be evaluated for their effects on T-cell dependent immunoglobulin responses and isotype switching. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Maliszewski, J. Immunol. 144:3028-3033, 1990; Mond, J.J. and Brunswick, M Assays for B Cell Function: *In vitro* Antibody Production, Vol 1 pp. 3.8.1-3.8.16 in Current Protocols in Immunology. J.E. Coligan et al Eds., John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be evaluated for their effect on immune effector cells, including their effect on Th1 cells and cytotoxic lymphocytes. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte

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Function 3.1-3.19) and Chapter 7 (Immunologic Studies in Humans) in Current Protocols in Immunology, J.E. Coligan et al. Eds., Greene Publishing Associates and Wiley-Interscience; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al.; J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

The proteins encoded by the cDNAs may also be evaluated for their effect on dendritic cell mediated activation of naive T-cells. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

The proteins ercoded by the cDNAs may also be evaluated for their influence on the lifetime of lymphocytes.

Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Those proteins which exhibit activity as immune system regulators activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of immune activity is beneficial. For example, the protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis,

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myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

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Using the proteins of the invention it may also be possible to regulate immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T-cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. 10 Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte 15 antigen functions (such as, for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 20 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an 25 immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed 30 using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4lg fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models

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of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which 5 promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead 10 to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/pr/pr mice or NZB hybrid mice, murine autoimmuno collagen arthritis, diabetes mellitus in OD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory 20 form of B lymphocyte antigens systemically.

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Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to T cells 25 in vivo, thereby activating the T cells.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be 30 transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

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The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acids encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β₂ macroglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class II or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor specific tolerance in the subject. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 34

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Hematopoiesis Regulating Activity

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their hematopoiesis regulating activity. For example, the effect of the proteins on embryonic stem cell differentiation may be evaluated. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their influence on the lifetime of stem cells and stem cell differentiation. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Freshney, M.G. Methylcellulose Colony Forming Assays, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; McNiece, I.K. and Briddell, R.A. Primitive Hematopoietic Colony Forming Cells with High Proliferative Potential, in Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Ploemacher, R.E. Cobblestone Area Forming Cell Assay, In Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Spooncer, E., Dexter, M. and Allen, T. Long Term Bone Marrow Cultures in the Presence of Stromal Cells, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds.

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pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; and Sutherland, H.J. Long Term Culture Initiating Cell Assay, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Those proteins which exhibit hematopoiesis regulatory activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of hematopoeisis is beneficial. For example, a protein of the present 5 invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid 10 cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelosuppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem 15 cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantion, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or 20 genetically manipulated for gene therapy. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 35

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Regulation of Tissue Growth

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their effect on tissue growth. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in International Patent Publication No. W095/16035, International Patent Publication No. W095/05846 and International Patent Publication No. W091/07491.

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Assays for wound healing activity include, without limitation, those described in: Winter, <u>Epidermal Wound Healing</u>, pps. 71-112 (Maibach, H1 and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Those proteins which are involved in the regulation of tissue growth may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of tissue growth is beneficial. For example, a protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or

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nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and 5 other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair 10 processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

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Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to 20 tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate 25 growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

30 The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e., for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as

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Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium) muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to generate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokinc damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

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EXAMPLE 36

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Regulation of Reproductive Hormones or Cell Movement

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their ability to regulate reproductive hormones, such as follicle stimulating hormone. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986. Chapter 6.12 (Measurement of Alpha and Beta Chemokines) Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Intersciece; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al. Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153:1762-1768, 1994.

Those proteins which exhibit activity as reproductive hormones or regulators of cell movement may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of reproductive hormones or cell movement are beneficial. For example, a protein of the present invention may also exhibit activin- or inhibin-related

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activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of folic stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals.

Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-B group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 36A

Assaying the Proteins Expressed from Extended cDNAs or

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Portions Thereof for Chemotactic/Chemokinetic Activity

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for chemotactic/chemokinetic activity. For example, a protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, cosinophils, epithelial and/or endothelial cells. Chemotactic and chmokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhension of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12,

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Measurement of alpha and beta Chemokincs 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Mueller et al Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol, 153:1762-1768, 1994.

EXAMPLE 37

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<u>Assaying the Proteins Expressed from Extended cDNAs or</u> <u>Portions Thereof for Regulation of Blood Clotting</u>

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their effects on blood clotting. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res.

45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Those proteins which are involved in the regulation of blood clotting may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of blood clotting is beneficial. For example, a protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulations disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as,for example, infarction of cardiac and central nervous system vessels (e.g., stroke). Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 38

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Involvement in Receptor/Ligand Interactions

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for their involvement in receptor/ligand interactions. Numerous assays for such involvement are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 7.28 (Measurement of Cellular Adhesion under Static Conditions 7.28.1-7.28.22) in Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience; Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160, 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995; Gyuris et al., Cell 75:791-803, 1993.

For example, the proteins of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion

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molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune respones). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

EXAMPLE 38A

Assaying the Proteins Expressed from Extended cDNAs or Portions

Thereof for Anti-Inflammatory Activity

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)),ischemia-reperfusioninury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

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EXAMPLE 38B

Assaying the Proteins Expressed from Extended cDNAs or

Portions Thereof for Tumor Inhibition Activity

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for tumor inhibition activity. In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, climinating or inhibiting factors, agents or cell types which promote tumor growth.

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or

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circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or climination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

EXAMPLE 39

Identification of Proteins which Interact with Polypeptides Encoded by Extended cDNAs

Proteins which interact with the polypeptides encoded by extended cDNAs or portions thereof, such as

receptor proteins, may be identified using two hybrid systems such as the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech). As described in the manual accompanying the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech), the extended cDNAs or portions thereof, are inserted into an expression vector such that they are in frame with DNA encoding the DNA binding domain of the yeast transcriptional activator GAL4. cDNAs in a cDNA library which encode proteins which might interact with the polypeptides encoded by the extended cDNAs or portions thereof

are inserted into a second expression vector such that they are in frame with DNA encoding the activation domain of GAL4. The two expression plasmids are transformed into yeast and the yeast are plated on selection medium which selects for expression of selectable markers on each of the expression vectors as well as GAL4 dependent expression of the HIS3 gene. Transformants capable of growing on medium lacking histidine are screened for GAL4 dependent lacZ expression. Those cells which are positive in both the histidine selection and the lacZ assay contain plasmids encoding proteins which interact with the polypeptide encoded by the extended cDNAs or portions thereof.

Alternatively, the system described in Lustig et al., Methods in Enzymology 283: 83-99 (1997) may be used for identifying molecules which interact with the polypeptides encoded by extended cDNAs. In such systems, *in vitro* transcription reactions are performed on a pool of vectors containing extended cDNA inserts cloned downstream of a promoter which drives *in vitro* transcription. The resulting pools of mRNAs are introduced into *Xenopus laevis* oocytes.

30 The oocytes are then assayed for a desired activity.

Alternatively, the pooled *in vitro* transcription products produced as described above may be translated *in vitro*. The pooled *in vitro* translation products can be assayed for a desired activity or for interaction with a known polypeptide.

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Proteins or other molecules interacting with polypeptides encoded by extended cDNAs can be found by a variety of additional techniques. In one method, affinity columns containing the polypeptide encoded by the extended cDNA or a portion thereof can be constructed. In some versions, of this method the affinity column contains chimeric proteins in which the protein encoded by the extended cDNA or a portion thereof is fused to glutathione S-transferase. 5 A mixture of cellular proteins or pool of expressed proteins as described above and is applied to the affinity column. Proteins interacting with the polypeptide attached to the column can then be isolated and analyzed on 2-D electrophoresis gel as described in Ramunsen et al. Electrophoresis, 18, 588-598 (1997). Alternatively, the proteins retained on the affinity column can be purified by electrophoresis based methods and sequenced. The same method can

be used to isolate antibodies, to screen phage display products, or to screen phage display human antibodies. Proteins interacting with polypeptides encoded by extended cDNAs or portions thereof can also be screened by using an Optical Biosensor as described in Edwards & Leatherbarrow, Analytical Biochemistry, 246, 1-6 (1997). The main advantage of the method is that it allows the determination of the association rate between the protein and other interacting molecules. Thus, it is possible to specifically select interacting molecules with a high or low association rate. Typically a target molecule is linked to the sensor surface (through a carboxymethl dextran matrix) and a sample of test 15 molecules is placed in contact with the target molecules. The binding of a test molecule to the target molecule causes a change in the refractive index and/ or thickness. This change is detected by the Biosensor provided it occurs in the evanescent field (which extend a few hundred manometers from the sensor surface). In these screening assays, the target molecule can be one of the polypeptides encoded by extended cDNAs or a portion thereof and the test sample can be a collection of proteins extracted from tissues or cells, a pool of expressed proteins, combinatorial peptide and/ or 20 chemical libraries, or phage displayed peptides. The tissues or cells from which the test proteins are extracted can originate from any species.

In other methods, a target protein is immobilized and the test population is a collection of unique polypeptides encoded by the extended cDNAs or portions thereof.

To study the interaction of the proteins encoded by the extended cDNAs or portions thereof with drugs, the 25 microdialysis coupled to HPLC method described by Wang et al., Chromatographia, 44, 205-208(1997) or the affinity capillary electrophoresis method described by Busch et al., J. Chromatogr. 777:311-328 (1997), the disclosures of which are incorporated herein by referenc can be used.

The system described in U.S. Patent No. 5,654,150 may also be used to identify molecules which interact with the polypeptides encoded by the extended cDNAs. In this system, pools of extended cDNAs are transcribed and 30 translated in vitro and the reaction products are assayed for interaction with a known polypeptide or antibody.

It will be appreciated by those skilled in the art that the proteins expressed from the extended cDNAs or portions may be assayed for numerous activities in addition to those specifically enumerated above. For example, the expressed proteins may be evaluated for applications involving control and regulation of inflammation, tumor

proliferation or metastasis, infection, or other clinical conditions. In addition, the proteins expressed from the extended cDNAs or portions thereof may be useful as nutritional agents or cosmetic agents.

The proteins expressed from the extended cDNAs or portions thereof may be used to generate antibodies capable of specifically binding to the expressed protein or fragments thereof as described in Example 40 below. The antibodies may capable of binding a full length protein encoded by one of the sequences of SEQ ID NOs. 40-140 and 242-377, a mature protein encoded by one of the sequences of SEQ ID NOs. 40-140 and 242-377. Alternatively, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 10 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In some embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 15 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 25 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In further embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 40 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513.

EXAMPLE 40

Production of an Antibody to a Human Protein

Substantially pure protein or polypeptide is isolated from the transfected or transformed cells as described in Example 30. The concentration of protein in the final preparation is adjusted, for example, by concentration on an Amicon filter device, to the level of a few micrograms/ml. Monoclonal or polyclonal antibody to the protein can then be prepared as follows:

A. Monoclonal Antibody Production by Hybridoma Fusion

Monoclonal antibody to epitopes of any of the peptides identified and isolated as described can be prepared from murine hybridomas according to the classical method of Kohler, G. and Milstein, C., Nature 256:495 (1975) or derivative methods thereof. Briefly, a mouse is repetitively inoculated with a few micrograms of the selected protein or peptides derived therefrom over a period of a few weeks. The mouse is then sacrificed, and the antibody producing cells of the spleen isolated. The spleen cells are fused by means of polyethylene glycol with mouse myeloma cells, and the excess unfused cells destroyed by growth of the system on selective media comprising aminopterin (HAT media). The successfully fused cells are diluted and aliquots of the dilution placed in wells of a microtiter plate where growth of the culture is continued. Antibody-producing clones are identified by detection of antibody in the supernatant fluid of the wells by immunoassay procedures, such as Elisa, as originally described by Engvall, E., Meth. Enzymol. 70:419 (1980), and derivative methods thereof. Selected positive clones can be expanded and their monoclonal antibody product harvested for use. Detailed procedures for monoclonal antibody production are described in Davis, L. et al. Basic Methods in Molecular Biology Elsevier, New York. Section 21-2.

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B. Polyclonal Antibody Production by Immunization

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Polyclonal antiserum containing antibodies to heterogenous epitopes of a single protein can be prepared by immunizing suitable animals with the expressed protein or peptides derived therefrom described above, which can be unmodified or modified to enhance immunogenicity. Effective polyclonal antibody production is affected by many factors 5 related both to the antigen and the host species. For example, small molecules tend to be less immunogenic than others and may require the use of carriers and adjuvant. Also, host animals vary in response to site of inoculations and dose, with both inadequate or excessive doses of antigen resulting in low titer antisera. Small doses (ng level) of antigen administered at multiple intradermal sites appears to be most reliable. An effective immunization protocol for rabbits can be found in Vaitukaitis, J. et al. J. Clin. Endocrinol. Metab. 33:988-991 (1971).

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Booster injections can be given at regular intervals, and antiserum harvested when antibody titer thereof, as determined semi-quantitatively, for example, by double immunodiffusion in agar against known concentrations of the antigen, begins to fall. See, for example, Ouchterlony, O. et al., Chap. 19 in: Handbook of Experimental Immunology D. Wier (ed) Blackwell (1973). Plateau concentration of antibody is usually in the range of 0.1 to 0.2 mg/ml of serum (about 12 μ M). Affinity of the antisera for the antigen is determined by preparing competitive binding curves, as 15 described, for example, by Fisher, D., Chap. 42 in: Manual of Clinical Immunology, 2d Ed. (Rose and Friedman, Eds.) Amer. Soc. For Microbiol., Washington, D.C. (1980).

Antibody preparations prepared according to either protocol are useful in quantitative immunoassays which determine concentrations of antigen-bearing substances in biological samples; they are also used semi-quantitatively or qualitatively to identify the presence of antigen in a biological sample. The antibodies may also be used in therapeutic 20 compositions for killing cells expressing the protein or reducing the levels of the protein in the body.

V. Use of Extended cDNAs or Portions Thereof as Reagents

The extended cDNAs of the present invention may be used as reagents in isolation procedures, diagnostic assays, and forensic procedures. For example, sequences from the extended cDNAs (or genomic DNAs obtainable 25 therefrom) may be detectably labeled and used as probes to isolate other sequences capable of hybridizing to them. In addition, sequences from the extended cDNAs (or genomic DNAs obtainable therefrom) may be used to design PCR primers to be used in isolation, diagnostic, or forensic procedures.

EXAMPLE 41

Preparation of PCR Primers and Amplification of DNA

30 The extended cDNAs (or genomic DNAs obtainable therefrom) may be used to prepare PCR primers for a variety of applications, including isolation procedures for cloning nucleic acids capable of hybridizing to such sequences, diagnostic techniques and forensic techniques. The PCR primers are at least 10 bases, and preferably at least 12, 15, or 17 bases in length. More preferably, the PCR primers are at least 20-30 bases in length. In some embodiments, the PCR primers may be more than 30 bases in length. It is preferred that the primer pairs have approximately the same G/C

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ratio, so that melting temperatures are approximately the same. A variety of PCR techniques are familiar to those skilled in the art. For a review of PCR technology, see Molecular Cloning to Genetic Engineering White, B.A. Ed. in Methods in Molecular Biology 67: Humana Press, Totowa 1997. In each of these PCR procedures, PCR primers on either side of the nucleic acid sequences to be amplified are added to a suitably prepared nucleic acid sample along with dNTPs and a thermostable polymerase such as Taq polymerase, Pfu polymerase, or Vent polymerase. The nucleic acid in the sample is denatured and the PCR primers are specifically hybridized to complementary nucleic acid sequences in the sample. The hybridized primers are extended. Thereafter, another cycle of denaturation, hybridization, and extension is initiated. The cycles are repeated multiple times to produce an amplified fragment containing the nucleic acid sequence between the primer sites.

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EXAMPLE 42

Use of Extended cDNAs as Probes

Probes derived from extended cDNAs or portions thereof (or genomic DNAs obtainable therefrom) may be labeled with detectable labels familiar to those skilled in the art, including radioisotopes and non-radioactive labels, to provide a detectable probe. The detectable probe may be single stranded or double stranded and may be made using techniques known in the art, including in vitro transcription, nick translation, or kinase reactions. A nucleic acid sample containing a sequence capable of hybridizing to the labeled probe is contacted with the labeled probe. If the nucleic acid in the sample is double stranded, it may be denatured prior to contacting the probe. In some applications, the nucleic acid sample may be immobilized on a surface such as a nitrocellulose or nylon membrane. The nucleic acid sample may comprise nucleic acids obtained from a variety of sources, including genomic DNA, cDNA libraries, RNA, or tissue samples.

Procedures used to detect the presence of nucleic acids capable of hybridizing to the detectable probe include well known techniques such as Southern blotting, Northern blotting, dot blotting, colony hybridization, and plaque hybridization. In some applications, the nucleic acid capable of hybridizing to the labeled probe may be cloned into vectors such as expression vectors, sequencing vectors, or in vitro transcription vectors to facilitate the characterization and expression of the hybridizing nucleic acids in the sample. For example, such techniques may be used to isolate and clone sequences in a genomic library or cDNA library which are capable of hybridizing to the detectable probe as described in Example 30 above.

PCR primers made as described in Example 41 above may be used in forensic analyses, such as the DNA fingerprinting techniques described in Examples 43-47 below. Such analyses may utilize detectable probes or primers based on the sequences of the extended cDNAs isolated using the 5' ESTs (or genomic DNAs obtainable therefrom).

EXAMPLE 43

Forensic Matching by DNA Sequencing

In one exemplary method, DNA samples are isolated from forensic specimens of, for example, hair, semen, blood or skin cells by conventional methods. A panel of PCR primers based on a number of the extended cDNAs (or

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genomic DNAs obtainable therefrom), is then utilized in accordance with Example 41 to amplify DNA of approximately 100-200 bases in length from the forensic specimen. Corresponding sequences are obtained from a test subject. Each of these identification DNAs is then sequenced using standard techniques, and a simple database comparison determines the differences, if any, between the sequences from the subject and those from the sample. Statistically significant differences between the suspect's DNA sequences and those from the sample conclusively prove a lack of identity. This lack of identity can be proven, for example, with only one sequence. Identity, on the other hand, should be demonstrated with a large number of sequences, all matching. Preferably, a minimum of 50 statistically identical sequences of 100 bases in length are used to prove identity between the suspect and the sample.

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EXAMPLE 44

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Positive Identification by DNA Sequencing

The technique outlined in the previous example may also be used on a larger scale to provide a unique fingerprint-type identification of any individual. In this technique, primers are prepared from a large number of sequences from Table IV and the appended sequence listing. Preferably, 20 to 50 different primers are used. These primers are used to obtain a corresponding number of PCR-generated DNA segments from the individual in question in accordance with Example 41. Each of these DNA segments is sequenced, using the methods set forth in Example 43. The database of sequences generated through this procedure uniquely identifies the individual from whom the sequences were obtained. The same panel of primers may then be used at any later time to absolutely correlate tissue or other biological specimen with that individual.

EXAMPLE 45

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Southern Blot Forensic Identification

The procedure of Example 44 is repeated to obtain a panel of at least 10 amplified sequences from an individual and a specimen. Preferably, the panel contains at least 50 amplified sequences. More preferably, the panel contains 100 amplified sequences. In some embodiments, the panel contains 200 amplified sequences. This PCR-generated DNA is then digested with one or a combination of, preferably, four base specific restriction enzymes. Such enzymes are commercially available and known to those of skill in the art. After digestion, the resultant gene fragments are size separated in multiple duplicate wells on an agarose gel and transferred to nitrocellulose using Southern blotting techniques well known to those with skill in the art. For a review of Southern blotting see Davis et al. (Basic Methods in Molecular Biology, 1986, Elsevier Press. pp 62-65).

A panel of probes based on the sequences of the extended cDNAs (or genomic DNAs obtainable therefrom), or fragments thereof of at least 10 bases, are radioactively or colorimetrically labeled using methods known in the art, such as nick translation or end labeling, and hybridized to the Southern blot using techniques known in the art (Davis et al., supra). Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30

nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom).

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Preferably, at least 5 to 10 of these labeled probes are used, and more preferably at least about 20 or 30 are 5 used to provide a unique pattern. The resultant bands appearing from the hybridization of a large sample of extended cDNAs (or genomic DNAs obtainable therefrom) will be a unique identifier. Since the restriction enzyme cleavage will be different for every individual, the band pattern on the Southern blot will also be unique. Increasing the number of extended cDNA probes will provide a statistically higher level of confidence in the identification since there will be an increased number of sets of bands used for identification.

10 **EXAMPLE 46**

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Dot Blot Identification Procedure

Another technique for identifying individuals using the extended cDNA sequences disclosed herein utilizes a dot blot hybridization technique.

Genomic DNA is isolated from nuclei of subject to be identified. Oligonucleotide probes of approximately 30 bp 15 in length are synthesized that correspond to at least 10, preferably 50 sequences from the extended cDNAs or genomic DNAs obtainable therefrom. The probes are used to hybridize to the genomic DNA through conditions known to those in the art. The oligonucleotides are end labeled with P32 using polynucleotide kinase (Pharmacia). Dot Blots are created by spotting the genomic DNA onto nitrocellulose or the like using a vacuum dot blot manifold (BioRad, Richmond California). The nitrocellulose filter containing the genomic sequences is baked or UV linked to the filter, prehybridized and 20 hybridized with labeled probe using techniques known in the art (Davis et al. supra). The 32P labeled DNA fragments are sequentially hybridized with successively stringent conditions to detect minimal differences between the 30 bp sequence and the DNA. Tetramethylammonium chloride is useful for identifying clones containing small numbers of nucleotide mismatches (Wood et al., Proc. Natl. Acad. Sci. USA 82(6):1585-1588 (1985)). A unique pattern of dots distinguishes one individual from another individual.

Extended cDNAs or oligonucleotides containing at least 10 consecutive bases from these sequences can be used as probes in the following alternative fingerprinting technique. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30 nucleotides from the extended cDNA (or genomic 30 DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom).

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Preferably, a plurality of probes having sequences from different genes are used in the alternative fingerprinting technique. Example 47 below provides a representative alternative fingerprinting procedure in which the probes are derived from extended cDNAs.

EXAMPLE 47

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Alternative "Fingerprint" Identification Technique

20-mer oligonucleotides are prepared from a large number, e.g. 50, 100, or 200, of extended cDNA sequences (or genomic DNAs obtainable therefrom) using commercially available oligonucleotide services such as Genset, Paris, France. Cell samples from the test subject are processed for DNA using techniques well known to those with skill in the art. The nucleic acid is digested with restriction enzymes such as EcoRI and Xbal. Following digestion, samples are applied to wells for electrophoresis. The procedure, as known in the art, may be modified to accommodate polyacrylamide electrophoresis, however in this example, samples containing 5 ug of DNA are loaded into wells and separated on 0.8% agarose gels. The gels are transferred onto nitrocellulose using standard Southern blotting techniques.

10 ng of each of the oligonucleotides are pooled and end-labeled with P³². The nitrocellulose is prehybridized
with blocking solution and hybridized with the labeled probes. Following hybridization and washing, the nitrocellulose
filter is exposed to X-Omat AR X-ray film. The resulting hybridization pattern will be unique for each individual.

It is additionally contemplated within this example that the number of probe sequences used can be varied for additional accuracy or clarity.

The antibodies generated in Examples 30 and 40 above may be used to identify the tissue type or cell species 20 from which a sample is derived as described above.

EXAMPLE 48

Identification of Tissue Types or Cell Species by Means of

Labeled Tissue Specific Antibodies

Identification of specific tissues is accomplished by the visualization of tissue specific antigens by means of
antibody preparations according to Examples 30 and 40 which are conjugated, directly or indirectly to a detectable
marker. Selected labeled antibody species bind to their specific antigen binding partner in tissue sections, cell
suspensions, or in extracts of soluble proteins from a tissue sample to provide a pattern for qualitative or semiqualitative interpretation.

Antisera for these procedures must have a potency exceeding that of the native preparation, and for that
reason, antibodies are concentrated to a mg/ml level by isolation of the gamma globulin fraction, for example, by ionexchange chromatography or by ammonium sulfate fractionation. Also, to provide the most specific antisera, unwanted
antibodies, for example to common proteins, must be removed from the gamma globulin fraction, for example by means
of insoluble immunoabsorbents, before the antibodies are labeled with the marker. Either monoclonal or heterologous
antisera is suitable for either procedure.

A. Immunohistochemical Techniques

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Purified, high-titer antibodies, prepared as described above, are conjugated to a detectable marker, as described, for example, by Fudenberg, H., Chap. 26 in: Basic 503 Clinical Immunology, 3rd Ed. Lange, Los Altos, California (1980) or Rose, N. et al., Chap. 12 in: Methods in Immunodiagnosis, 2d Ed. John Wiley 503 Sons, New York (1980).

A fluorescent marker, either fluorescein or rhodamine, is preferred, but antibodies can also be labeled with an enzyme that supports a color producing reaction with a substrate, such as horseradish peroxidase. Markers can be added to tissue-bound antibody in a second step, as described below. Alternatively, the specific antitissue antibodies can be labeled with ferritin or other electron dense particles, and localization of the ferritin coupled antigen-antibody complexes achieved by means of an electron microscope. In yet another approach, the antibodies are radiolabeled, with, for example 1251, and detected by overlaying the antibody treated preparation with photographic emulsion.

Preparations to carry out the procedures can comprise monoclonal or polyclonal antibodies to a single protein or peptide identified as specific to a tissue type, for example, brain tissue, or antibody preparations to several antigenically distinct tissue specific antigens can be used in panels, independently or in mixtures, as required.

Tissue sections and cell suspensions are prepared for immunohistochemical examination according to common histological techniques. Multiple cryostat sections (about 4 µm, unfixed) of the unknown tissue and known control, are mounted and each slide covered with different dilutions of the antibody preparation. Sections of known and unknown tissues should also be treated with preparations to provide a positive control, a negative control, for example, pre-immune sera, and a control for non-specific staining, for example, buffer.

Treated sections are incubated in a humid chamber for 30 min at room temperature, rinsed, then washed in buffer for 30-45 min. Excess fluid is blotted away, and the marker developed.

If the tissue specific antibody was not labeled in the first incubation, it can be labeled at this time in a second antibody-antibody reaction, for example, by adding fluorescein- or enzyme-conjugated antibody against the immunoglobulin class of the antiserum-producing species, for example, fluorescein labeled antibody to mouse IgG. Such 25 labeled sera are commercially available.

The antigen found in the tissues by the above procedure can be quantified by measuring the intensity of color or fluorescence on the tissue section, and calibrating that signal using appropriate standards.

B. Identification of Tissue Specific Soluble Proteins

The visualization of tissue specific proteins and identification of unknown tissues from that procedure is

carried out using the labeled antibody reagents and detection strategy as described for immunohistochemistry; however
the sample is prepared according to an electrophoretic technique to distribute the proteins extracted from the tissue in
an orderly array on the basis of molecular weight for detection.

A tissue sample is homogenized using a Virtis apparatus; cell suspensions are disrupted by Dounce homogenization or osmotic lysis, using detergents in either case as required to disrupt cell membranes, as is the practice

in the art. Insoluble cell components such as nuclei, microsomes, and membrane fragments are removed by ultracentrifugation, and the soluble protein-containing fraction concentrated if necessary and reserved for analysis.

A sample of the soluble protein solution is resolved into individual protein species by conventional SDS polyacrylamide electrophoresis as described, for example, by Davis, L. et al., Section 19-2 in: Basic Methods in 5 Molecular Biology (P. Leder, ed), Elsevier, New York (1986), using a range of amounts of polyacrylamide in a set of gels to resolve the entire molecular weight range of proteins to be detected in the sample. A size marker is run in parallel for purposes of estimating molecular weights of the constituent proteins. Sample size for analysis is a convenient volume of from 5 to 55 μ l, and containing from about 1 to 100 μ g protein. An aliquot of each of the resolved proteins is transferred by blotting to a nitrocellulose filter paper, a process that maintains the pattern of resolution. Multiple copies 10 are prepared. The procedure, known as Western Blot Analysis, is well described in Davis, L. et al., (above) Section 19-3. One set of nitrocellulose blots is stained with Coomassie Blue dye to visualize the entire set of proteins for comparison with the antibody bound proteins. The remaining nitrocellulose filters are then incubated with a solution of one or more specific antisera to tissue specific proteins prepared as described in Examples 30 and 40. In this procedure, as in procedure A above, appropriate positive and negative sample and reagent controls are run.

In either procedure A or B, a detectable label can be attached to the primary tissue antigen-primary antibody complex according to various strategies and permutations thereof. In a straightforward approach, the primary specific antibody can be labeled; alternatively, the unlabeled complex can be bound by a labeled secondary anti-IgG antibody. In other approaches, either the primary or secondary antibody is conjugated to a biotin molecule, which can, in a subsequent step, bind an avidin conjugated marker. According to yet another strategy, enzyme labeled or radioactive 20 protein A, which has the property of binding to any IgG, is bound in a final step to either the primary or secondary antibody.

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The visualization of tissue specific antigen binding at levels above those seen in control tissues to one or more tissue specific antibodies, prepared from the gene sequences identified from extended cDNA sequences, can identify tissues of unknown origin, for example, forensic samples, or differentiated tumor tissue that has metastasized to foreign 25 bodily sites.

In addition to their applications in forensics and identification, extended cDNAs (or genomic DNAs obtainable therefrom) may be mapped to their chromosomal locations. Example 49 below describes radiation hybrid (RH) mapping of human chromosomal regions using extended cDNAs. Example 50 below describes a representative procedure for mapping an extended cDNA (or a genomic DNA obtainable therefrom) to its location on a human chromosome. Example 30 51 below describes mapping of extended cDNAs (or genomic DNAs obtainable therefrom) on metaphase chromosomes by Fluorescence In Situ Hybridization (FISH).

EXAMPLE 49

Radiation hybrid mapping of Extended cDNAs to the human genome

Radiation hybrid (RH) mapping is a somatic cell genetic approach that can be used for high resolution mapping of the human genome. In this approach, cell lines containing one or more human chromosomes are lethally irradiated, breaking each chromosome into fragments whose size depends on the radiation dose. These fragments are rescued by fusion with cultured rodent cells, yielding subclones containing different portions of the human genome. This technique is described by Benham et al. (*Genomics* 4:509-517, 1989) and Cox et al., (*Science* 250:245-250, 1990). The random and independent nature of the subclones permits efficient mapping of any human genome marker. Human DNA isolated from a panel of 80-100 cell lines provides a mapping reagent for ordering extended cDNAs (or genomic DNAs obtainable therefrom). In this approach, the frequency of breakage between markers is used to measure distance, allowing construction of fine resolution maps as has been done using conventional ESTs (Schuler et al., *Science* 274:540-546, 1996).

RH mapping has been used to generate a high-resolution whole genome radiation hybrid map of human chromosome 17q22-q25.3 across the genes for growth hormone (GH) and thyr.iidine kinase (TK) (Foster et al., *Genomics* 33:185-192, 1996), the region surrounding the Gorlin syndrome gene (Obermayr et al., *Eur. J. Hum. Genet.* 4:242-245, 1996), 60 loci covering the entire short arm of chromosome 12 (Raeymaekers et al., *Genomics* 29:170-178, 1995), the region of human chromosome 22 containing the neurofibromatosis type 2 locus (Frazer et al., *Genomics* 14:574-584, 1992) and 13 loci on the long arm of chromosome 5 (Warrington et al., *Genomics* 11:701-708, 1991).

EXAMPLE 50

Mapping of Extended cDNAs to Human

Chromosomes using PCR techniques

Extended cDNAs (or genomic DNAs obtainable therefrom) may be assigned to human chromosomes using PCR based methodologies. In such approaches, oligonucleotide primer pairs are designed from the extended cDNA sequence (or the sequence of a genomic DNA obtainable therefrom) to minimize the chance of amplifying through an intron. Preferably, the oligonucleotide primers are 18-23 bp in length and are designed for PCR amplification. The creation of PCR primers from known sequences is well known to those with skill in the art. For a review of PCR technology see Erlich, H.A., PCR Technology; Principles and Applications for DNA Amplification. 1992. W.H. Freeman and Co., New York.

The primers are used in polymerase chain reactions (PCR) to amplify templates from total human genomic DNA. PCR conditions are as follows: 60 ng of genomic DNA is used as a template for PCR with 80 ng of each oligonucleotide primer, 0.6 unit of Taq polymerase, and 1 µCu of a ³²P-labeled deoxycytidine triphosphate. The PCR is performed in a microplate thermocycler (Techne) under the following conditions: 30 cycles of 94°C, 1.4 min; 55°C, 2 min; and 72°C, 2 min; with a final extension at 72°C for 10 min. The amplified products are analyzed on a 6% polyacrylamide sequencing gel and visualized by autoradiography. If the length of the resulting PCR product is identical to the distance between the ends of the primer sequences in the extended cDNA from which the primers are derived, then the PCR reaction is repeated with DNA templates from two panels of human-rodent somatic cell hybrids, BIOS

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PCR is used to screen a series of somatic cell hybrid cell lines containing defined sets of human chromosomes for the presence of a given extended cDNA (or genomic DNA obtainable therefrom). DNA is isolated from the somatic hybrids and used as starting templates for PCR reactions using the primer pairs from the extended cDNAs (or genomic DNAs obtainable therefrom). Only those somatic cell hybrids with chromosomes containing the human gene corresponding to the extended cDNA (or genomic DNA obtainable therefrom) will yield an amplified fragment. The extended cDNAs (or genomic DNAs obtainable therefrom) are assigned to a chromosome by analysis of the segregation pattern of PCR products from the somatic hybrid DNA templates. The single human chromosome present in all cell hybrids that give rise to an amplified fragment is the chromosome containing that extended cDNA (or genomic DNA obtainable therefrom). For a review of techniques and analysis of results from somatic cell gene mapping experiments. (See Ledbetter et al., Genomics 6:475-481 (1990).)

Alternatively, the extended cDNAs (or genomic DNAs obtainable therefrom) may be mapped to individual chromosomes using FISH as described in Example 51 below.

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EXAMPLE 51

Mapping of Extended 5' ESTs to Chromosomes

Using Fluorescence in situ Hybridization

Fluorescence in situ hybridization allows the extended cDNA (or genomic DNA obtainable therefrom) to be mapped to a particular location on a given chromosome. The chromosomes to be used for fluorescence in situ hybridization techniques may be obtained from a variety of sources including cell cultures, tissues, or whole blood.

In a preferred embodiment, chromosomal localization of an extended cDNA (or genomic DNA obtainable therefrom) is obtained by FISH as described by Cherif et al. (*Proc. Natl. Acad. Sci. U.S.A.*, 87:6639-6643, 1990).

Metaphase chromosomes are prepared from phytohemagglutinin (PHA)-stimulated blood cell donors. PHA-stimulated lymphocytes from healthy males are cultured for 72 h in RPMI-1640 medium. For synchronization, methotrexate (10 µM) is added for 17 h, followed by addition of 5-bromodeoxyuridine (5-BudR, 0.1 mM) for 6 h. Colcemid (1 µg/ml) is added for the last 15 min before harvesting the cells. Cells are collected, washed in RPMI, incubated with a hypotonic solution of KCI (75 mM) at 37°C for 15 min and fixed in three changes of methanol:acetic acid (3:1). The cell suspension is dropped onto a glass slide and air dried. The extended cDNA (or genomic DNA obtainable therefrom) is labeled with biotin-16 dUTP by nick translation according to the manufacturer's instructions (Bethesda Research Laboratories, Bethesda, MD), purified using a Sephadex G-50 column (Pharmacia, Upssala, Sweden) and precipitated. Just prior to hybridization, the DNA pellet is dissolved in hybridization buffer (50% formamide, 2 X SSC, 10% dextran sulfate, 1 mg/ml sonicated salmon sperm DNA, pH 7) and the probe is denatured at 70°C for 5-10 min.

Slides kept at -20°C are treated for 1 h at 37°C with RNase A (100 μ g/ml), rinsed three times in 2 X SSC and dehydrated in an ethanol series. Chromosome preparations are denatured in 70% formamide, 2 X SSC for 2 min at

70°C, then dehydrated at 4°C. The slides are treated with proteinase K (10 μg/100 ml in 20 mM Tris-HCl, 2 mM CaCl₂) at 37°C for 8 min and dehydrated. The hybridization mixture containing the probe is placed on the slide, covered with a coverslip, sealed with rubber cement and incubated overnight in a humid chamber at 37°C. After hybridization and post-hybridization washes, the biotinylated probe is detected by avidin-FITC and amplified with additional layers of
5 biotinylated goat anti-avidin and avidin-FITC. For chromosomal localization, fluorescent R-bands are obtained as previously described (Cherif et al., supra.). The slides are observed under a LEICA fluorescence microscope (DMRXA). Chromosomes are counterstained with propidium iodide and the fluorescent signal of the probe appears as two symmetrical yellow-green spots on both chromatids of the fluorescent R-band chromosome (red). Thus, a particular extended cDNA (or genomic DNA obtainable therefrom) may be localized to a particular cytogenetic R-band on a given
10 chromosome.

Once the extended cDNAs (or genomic DNAs obtainable therefrom) have been assigned to particular chromosomes using the techniques described in Examples 49-51 above, they may be utilized to construct a high resolution map of the chromosomes on which they are located or to identify the chromosomes in a sample.

EXAMPLE 52

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Use of Extended cDNAs to Construct or Expand Chromosome Maps

Chromosome mapping involves assigning a given unique sequence to a particular chromosome as described above. Once the unique sequence has been mapped to a given chromosome, it is ordered relative to other unique sequences located on the same chromosome. One approach to chromosome mapping utilizes a series of yeast artificial chromosomes (YACs) bearing several thousand long inserts derived from the chromosomes of the organism from which the extended cDNAs (or genomic DNAs obtainable therefrom) are obtained. This approach is described in Ramaiah Nagaraja et al. Genome Research 7:210-222, March 1997. Briefly, in this approach each chromosome is broken into overlapping pieces which are inserted into the YAC vector. The YAC inserts are screened using PCR or other methods to determine whether they include the extended cDNA (or genomic DNA obtainable therefrom) whose position is to be determined. Once an insert has been found which includes the extended cDNA (or genomic DNA obtainable therefrom), the insert can be analyzed by PCR or other methods to determine whether the insert also contains other sequences known to be on the chromosome or in the region from which the extended cDNA (or genomic DNA obtainable therefrom) was derived. This process can be repeated for each insert in the YAC library to determine the location of each of the extended cDNAs (or genomic DNAs obtainable therefrom) relative to one another and to other known chromosomal markers. In this way, a high resolution map of the distribution of numerous unique markers along each of the organisms of thromosomes may be obtained.

As described in Example 53 below extended cDNAs (or genomic DNAs obtainable therefrom) may also be used to identify genes associated with a particular phenotype, such as hereditary disease or drug response.

EXAMPLE 53

Identification of genes associated with hereditary diseases or drug response

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This example illustrates an approach useful for the association of extended cDNAs (or genomic DNAs obtainable therefrom) with particular phenotypic characteristics. In this example, a particular extended cDNA (or genomic DNA obtainable therefrom) is used as a test probe to associate that extended cDNA (or genomic DNA obtainable therefrom) with a particular phenotypic characteristic.

Extended cDNAs (or genomic DNAs obtainable therefrom) are mapped to a particular location on a human chromosome using techniques such as those described in Examples 49 and 50 or other techniques known in the art. A search of Mendelian Inheritance in Man (V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) reveals the region of the human chromosome which contains the extended cDNA (or genomic DNA obtainable therefrom) to be a very gene rich region containing several known genes and several 10 diseases or phenotypes for which genes have not been identified. The gene corresponding to this extended cDNA (or genomic DNA obtainable therefrom) thus becomes an immediate candidate for each of these genetic diseases.

Cells from patients with these diseases or phenotypes are isolated and expanded in culture. PCR primers from the extended cDNA (or genomic DNA obtainable therefrom) are used to screen genomic DNA, mRNA or cDNA obtained from the patients. Extended cDNAs (or genomic DNAs obtainable therefrom) that are not amplified in the patients can 15 be positively associated with a particular disease by further analysis. Alternatively, the PCR analysis may yield fragments of different lengths when the samples are derived from an individual having the phenotype associated with the disease than when the sample is derived from a healthy individual, indicating that the gene containing the extended cDNA may be responsible for the genetic disease.

VI. Use of Extended cDNAs (or genomic DNAs obtainable therefrom) to Construct Vectors

The present extended cDNAs (or genomic DNAs obtainable therefrom) may also be used to construct secretion vectors capable of directing the secretion of the proteins encoded by genes inserted in the vectors. Such secretion vectors may facilitate the purification or enrichment of the proteins encoded by genes inserted therein by reducing the number of background proteins from which the desired protein must be purified or enriched. Exemplary secretion vectors are described in Example 54 below.

25 **EXAMPLE 54**

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Construction of Secretion Vectors

The secretion vectors of the present invention include a promoter capable of directing gene expression in the host cell, tissue, or organism of interest. Such promoters include the Rous Sarcoma Virus promoter, the SV40 promoter, the human cytomegalovirus promoter, and other promoters familiar to those skilled in the art.

A signal sequence from an extended cDNA (or genomic DNA obtainable therefrom), such as one of the signal sequences in SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above, is operably linked to the promoter such that the mRNA transcribed from the promoter will direct the translation of the signal peptide. The host cell, tissue, or organism may be any cell, tissue, or organism which recognizes the signal peptide encoded by the signal sequence in the WO 99/31236

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extended cDNA (or genomic DNA obtainable therefrom). Suitable hosts include mammalian cells, tissues or organisms; avian cells, tissues, or organisms, insect cells, tissues or organisms, or yeast.

In addition, the secretion vector contains cloning sites for inserting genes encoding the proteins which are to be secreted. The cloning sites facilitate the cloning of the insert gene in frame with the signal sequence such that a fusion 5 protein in which the signal peptide is fused to the protein encoded by the inserted gene is expressed from the mRNA transcribed from the promoter. The signal peptide directs the extracellular secretion of the fusion protein.

The secretion vector may be DNA or RNA and may integrate into the chromosome of the host, be stably maintained as an extrachromosomal replicon in the host, be an artificial chromosome, or be transiently present in the host. Many nucleic acid backbones suitable for use as secretion vectors are known to those skilled in the art, including 10 retroviral vectors, SV40 vectors, Bovine Papilloma Virus vectors, yeast integrating plasmids, yeast episomal plasmids, yeast artificial chromosomes, human artificial chromosomes, P element vectors, baculovirus vectors, or bacterial plasmids capable of being transiently introduced into the host.

The secretion vector may also contain a polyA signal such that the polyA signal is located downstream of the gene inserted into the secretion vector.

After the gene encoding the protein for which secretion is desired is inserted into the secretion vector, the secretion vector is introduced into the host cell, tissue, or organism using calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection, viral particles or as naked DNA. The protein encoded by the inserted gene is then purified or enriched from the supernatant using conventional techniques such as ammonium sulfate precipitation, immunoprecipitation, immunochromatography, size exclusion chromatography, ion exchange 20 chromatography, and hole. Alternatively, the secreted protein may be in a sufficiently enriched or pure state in the supernatant or growth media of the host to permit it to be used for its intended purpose without further enrichment.

The signal sequences may also be inserted into vectors designed for gene therapy. In such vectors, the signal sequence is operably linked to a promoter such that mRNA transcribed from the promoter encodes the signal peptide. A cloning site is located downstream of the signal sequence such that a gene encoding a protein whose secretion is 25 desired may readily be inserted into the vector and fused to the signal sequence. The vector is introduced into an appropriate host cell. The protein expressed from the promoter is secreted extracellularly, thereby producing a therapeutic effect.

The extended cDNAs or 5' ESTs may also be used to clone sequences located upstream of the extended cDNAs or 5' ESTs which are capable of regulating gene expression, including promoter sequences, enhancer sequences, and 30 other upstream sequences which influence transcription or translation levels. Once identified and cloned, these upstream regulatory sequences may be used in expression vectors designed to direct the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative fashion. Example 55 describes a method for cloning sequences upstream of the extended cDNAs or 5' ESTs.

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Use of Extended cDNAs or 5' ESTs to Clone Upstream

Sequences from Genomic DNA

Sequences derived from extended cDNAs or 5' ESTs may be used to isolate the promoters of the corresponding genes using chromosome walking techniques. In one chromosome walking technique, which utilizes the 5 GenomeWalkerTM kit available from Clontech, five complete genomic DNA samples are each digested with a different restriction enzyme which has a 6 base recognition site and leaves a blunt end. Following digestion, oligonucleotide adapters are ligated to each end of the resulting genomic DNA fragments.

For each of the five genomic DNA libraries, a first PCR reaction is performed according to the manufacturer's instructions using an outer adaptor primer provided in the kit and an outer gene specific primer. The gene specific primer 10 should be selected to be specific for the extended cDNA or 5' EST of interest and should have a melting temperature, length, and location in the extended cDNA or 'EST which is consistent with its use in PCR reactions. Each first PCR reaction contains 5ng of genomic DNA, 5 μ l of 10X Tth reaction buffer, 0.2 mM of each dNTP, 0.2 μ M each of outer adaptor primer and outer gene specific primer, 1.1 mM of Mg(OAc)₂, and 1 μ l of the Tth polymerase 50X mix in a total volume of 50 μ l. The reaction cycle for the first PCR reaction is as follows: 1 min @ 94°C / 2 sec @ 94°C, 3 min @ 15 72°C (7 cycles) / 2 sec @ 94°C, 3 min @ 67°C (32 cycles) / 5 min @ 67°C.

The product of the first PCR reaction is diluted and used as a template for a second PCR reaction according to the manufacturer's instructions using a pair of nested primers which are located internally on the amplicon resulting from the first PCR reaction. For example, 5 μ l of the reaction product of the first PCR reaction mixture may be diluted 180 times. Reactions are made in a 50 μ l volume having a composition identical to that of the first PCR reaction except 20 the nested primers are used. The first nested primer is specific for the adaptor, and is provided with the GenomeWalker™ kit. The second nested primer is specific for the particular extended cDNA or 5' EST for which the promoter is to be cloned and should have a melting temperature, length, and location in the extended cDNA or 5' EST which is consistent with its use in PCR reactions. The reaction parameters of the second PCR reaction are as follows: 1 min @ 94°C / 2 sec @ 94°C, 3 min @ 72°C (6 cycles) / 2 sec @ 94°C, 3 min @ 67°C (25 cycles) / 5 min @ 67°C

The product of the second PCR reaction is purified, cloned, and sequenced using standard techniques. Alternatively, two or more human genomic DNA libraries can be constructed by using two or more restriction enzymes. The digested genomic DNA is cloned into vectors which can be converted into single stranded, circular, or linear DNA. A biotinylated oligonucleotide comprising at least 15 nucleotides from the extended cDNA or 5' EST sequence is hybridized to the single stranded DNA. Hybrids between the biotinylated oligonucleotide and the single stranded DNA containing 30 the extended cDNA or EST sequence are isolated as described in Example 29 above. Thereafter, the single stranded DNA containing the extended cDNA or EST sequence is released from the beads and converted into double stranded DNA using a primer specific for the extended cDNA or 5' EST sequence or a primer corresponding to a sequence included in the cloning vector. The resulting double stranded DNA is transformed into bacteria. DNAs containing the 5' EST or extended cDNA sequences are identified by colony PCR or colony hybridization.

Once the upstream genomic sequences have been cloned and sequenced as described above, prospective promoters and transcription start sites within the upstream sequences may be identified by comparing the sequences upstream of the extended cDNAs or 5' ESTs with databases containing known transcription start sites, transcription factor binding sites, or promoter sequences.

In addition, promoters in the upstream sequences may be identified using promoter reporter vectors as 5 described in Example 56.

EXAMPLE 56

Identification of Promoters in Cloned Upstream Sequences

The genomic sequences upstream of the extended cDNAs or 5' ESTs are cloned into a suitable promoter 10 reporter vector, such as the pSEAP-Basic, pSEAP-Enhancer, pβgal-Basic, pβgal-Enhancer, or pEGFP-1 Promoter Reporter vectors available from Clontech. Briefly, each of these promoter reporter vectors include multiple cloning sites positioned upstream of a reporter gene encoding a readily assayable protein such as secreted alkaline phosphatase, β galactosidase, or green fluorescent protein. The sequences upstream of the extended cDNAs or 5' ESTs are inserted into the cloning sites upstream of the reporter gene in both orientations and introduced into an appropriate host cell. The 15 level of reporter protein is assayed and compared to the level obtained from a vector which lacks an insert in the cloning site. The presence of an elevated expression level in the vector containing the insert with respect to the control vector indicates the presence of a promoter in the insert. If necessary, the upstream sequences can be cloned into vectors which contain an enhancer for augmenting transcription levels from weak promoter sequences. A significant level of expression above that observed with the vector lacking an insert indicates that a promoter sequence is present in the 20 inserted upstream sequence.

Appropriate host cells for the promoter reporter vectors may be chosen based on the results of the above described determination of expression patterns of the extended cDNAs and ESTs. For example, if the expression pattern analysis indicates that the mRNA corresponding to a particular extended cDNA or 5' EST is expressed in fibroblasts, the promoter reporter vector may be introduced into a human fibroblast cell line.

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Promoter sequences within the upstream genomic DNA may be further defined by constructing nested deletions in the upstream DNA using conventional techniques such as Exonuclease III digestion. The resulting deletion fragments can be inserted into the promoter reporter vector to determine whether the deletion has reduced or obliterated promoter activity. In this way, the boundaries of the promoters may be defined. If desired, potential individual regulatory sites within the promoter may be identified using site directed mutagenesis or linker scanning to obliterate 30 potential transcription factor binding sites within the promoter individually or in combination. The effects of these mutations on transcription levels may be determined by inserting the mutations into the cloning sites in the promoter reporter vectors.

EXAMPLE 57

Cloning and Identification of Promoters

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Using the method described in Example 55 above with 5' ESTs, sequences upstream of several genes were obtained. Using the primer pairs GGG AAG ATG GAG ATA GTA TTG CCT G (SEQ ID NO:29) and CTG CCA TGT ACA TGA TAG AGA GAT TC (SEQ ID NO:30), the promoter having the internal designation P13H2 (SEQ ID NO:31) was obtained.

Using the primer pairs GTA CCA GGGG ACT GTG ACC ATT GC (SEQ ID NO:32) and CTG TGA CCA TTG CTC CCA AGA GAG (SEQ ID NO:33), the promoter having the internal designation P15B4 (SEQ ID NO:34) was obtained.

Using the primer pairs CTG GGA TGG AAG GCA CGG TA (SEQ ID NO:35) and GAG ACC ACA CAG CTA GAC AA (SEQ ID NO:36), the promoter having the internal designation P29B6 (SEQ ID NO:37) was obtained.

Figure 8 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5' tags. The upstream sequences were screened for the presence of motifs resembling transcription factor binding sites or known transcription start sites using the computer program MatInspector release 2.0, August 1996.

Figure 9 describes the transcription factor binding sites present in each of these promoters. The columns labeled matrice provides the name of the MatInspector matrix used. The column labeled position provides the 5' postion of the promoter site. Numeration of the sequence starts from the transcription site as determined by matching the genomic sequence with the 5' EST sequence. The column labeled "orientation" indicates the DNA strand on which the site is found, with the + strand being the coding strand as determined by matching the genomic sequence with the sequence of the 5' EST. The column labeled "score" provides the MatInspector score found for this site. The column labeled "length" provides the length of the site in nucleotides. The column labeled "sequence" provides the sequence of the site found.

The promoters and other regulatory sequences located upstream of the extended cDNAs or 5' ESTs may be used to design expression vectors capable of directing the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative manner. A promoter capable of directing the desired spatial, temporal, developmental, and quantitative patterns may be selected using the results of the expression analysis described in Example 26 above. For example, if a promoter which confers a high level of expression in muscle is desired, the promoter sequence upstream of an extended cDNA or 5' EST derived from an mRNA which is expressed at a high level in muscle, as determined by the method of Example 26, may be used in the expression vector.

Preferably, the desired promoter is placed near multiple restriction sites to facilitate the cloning of the desired insert downstream of the promoter, such that the promoter is able to drive expression of the inserted gene. The promoter may be inserted in conventional nucleic acid backbones designed for extrachromosomal replication, integration into the host chromosomes or transient expression. Suitable backbones for the present expression vectors include retroviral backbones, backbones from eukaryotic episomes such as SV40 or Bovine Papilloma Virus, backbones from bacterial episomes, or artificial chromosomes.

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Preferably, the expression vectors also include a polyA signal downstream of the multiple restriction sites for directing the polyadenylation of mRNA transcribed from the gene inserted into the expression vector.

Following the identification of promoter sequences using the procedures of Examples 55-57, proteins which interact with the promoter may be identified as described in Example 58 below.

5 EXAMPLE 58

Identification of Proteins Which Interact with Promoter Sequences, Upstream

Regulatory Sequences, or mRNA

Sequences within the promoter region which are likely to bind transcription factors may be identified by homology to known transcription factor binding sites or through conventional mutagenesis or deletion analyses of reporter plasmids containing the promoter sequence. For example, deletions may be made in a reporter plasmid containing the promoter sequence of interest operably linked to an assayable reporter gene. The reporter plasmids carrying various deletions within the promoter region are transfected into an appropriate host cell and the effects of the deletions on expression levels is assessed. Transcription factor binding sites within the regions in which deletions reduce expression levels may be further localized using site directed mutagenesis, linker scanning analysis, or other techniques familiar to those skilled in the art. Nucleic acids encoding proteins which interact with sequences in the promoter may be identified using one-hybrid systems such as those described in the manual accompanying the Matchmaker One-hybrid System kit avalilabe from Clontech (Catalog No. K1603-1). Briefly, the Matchmaker One-hybrid system is used as follows. The target sequence for which it is desired to identify binding proteins is cloned upstream of a selectable reporter gene and integrated into the yeast genome. Preferably, multiple copies of the target sequences are inserted into the reporter plasmid in tandem.

A library comprised of fusions between cDNAs to be evaluated for the ability to bind to the promoter and the activation domain of a yeast transcription factor, such as GAL4, is transformed into the yeast strain containing the integrated reporter sequence. The yeast are plated on selective media to select cells expressing the selectable marker linked to the promoter sequence. The colonies which grow on the selective media contain genes encoding proteins which bind the target sequence. The inserts in the genes encoding the fusion proteins are further characterized by sequencing. In addition, the inserts may be inserted into expression vectors or in vitro transcription vectors. Binding of the polypeptides encoded by the inserts to the promoter DNA may be confirmed by techniques familiar to those skilled in the art, such as gel shift analysis or DNAse protection analysis.

VII. Use of Extended cDNAs (or Genomic DNAs Obtainable Therefrom) in Gene Therapy

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The present invention also comprises the use of extended cDNAs (or genomic DNAs obtainable therefrom) in gene therapy strategies, including antisense and triple helix strategies as described in Examples 57 and 58 below. In antisense approaches, nucleic acid sequences complementary to an mRNA are hybridized to the mRNA intracellularly, thereby blocking the expression of the protein encoded by the mRNA. The antisense sequences may prevent gene expression through a variety of mechanisms. For example, the antisense sequences may inhibit the ability of ribosomes

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to translate the mRNA. Alternatively, the antisense sequences may block transport of the mRNA from the nucleus to the cytoplasm, thereby limiting the amount of mRNA available for translation. Another mechanism through which antisense sequences may inhibit gene expression is by interfering with mRNA splicing. In yet another strategy, the antisense nucleic acid may be incorporated in a ribozyme capable of specifically cleaving the target mRNA.

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EXAMPLE 59

Preparation and Use of Antisense Oligonucleotides

The antisense nucleic acid molecules to be used in gene therapy may be either DNA or RNA sequences. They may comprise a sequence complementary to the sequence of the extended cDNA (or genomic DNA obtainable therefrom). The antisense nucleic acids should have a length and melting temperature sufficient to permit formation of an intracellular duplex having sufficient stability to inhibit the expression of the mRNA in the duplex. Strategies for designing antisense nucleic acids suitable for use in gene therapy are disclosed in Green et al., Ann. Rev. Biochem. 55:569-597 (1986) and Izant and Weintraub, Cell 36:1007-1015 (1984).

In some strategies, antisense molecules are obtained from a nucleotide sequence encoding a protein by reversing the orientation of the coding region with respect to a promoter so as to transcribe the opposite strand from that which is normally transcribed in the cell. The antisense molecules may be transcribed using in vitro transcription systems such as those which employ T7 or SP6 polymerase to generate the transcript. Another approach involves transcription of the antisense nucleic acids in vivo by operably linking DNA containing the antisense sequence to a promoter in an expression vector.

Alternatively, oligonucleotides which are complementary to the strand normally transcribed in the cell may be synthesized in vitro. Thus, the antisense nucleic acids are complementary to the corresponding mRNA and are capable of hybridizing to the mRNA to create a duplex. In some embodiments, the antisense sequences may contain modified sugar phosphate backbones to increase stability and make them less sensitive to RNase activity. Examples of modifications suitable for use in antisense strategies are described by Rossi et al., Pharmacol. Ther. 50(2):245-254, (1991).

Various types of antisense oligonucleotides complementary to the sequence of the extended cDNA (or genomic DNA obtainable therefrom) may be used. In one preferred embodiment, stable and semi-stable antisense oligonucleotides described in International Application No. PCT W094/23026 are used. In these molecules, the 3' end or both the 3' and 5' ends are engaged in intramolecular hydrogen bonding between complementary base pairs. These molecules are better able to withstand exonuclease attacks and exhibit increased stability compared to conventional antisense oligonucleotides.

In another preferred embodiment, the antisense oligodeoxynucleotides against herpes simplex virus types 1 and 2 described in International Application No. WO 95/04141.

In yet another preferred embodiment, the covalently cross-linked antisense oligonucleotides described in International Application No. WO 96/31523 are used. These double- or single-stranded oligonucleotides comprise one or WO 99/31236 PCT/IB98/02122 -84

more, respectively, inter- or intra-oligonucleotide covalent cross-linkages, wherein the linkage consists of an amide bond between a primary amine group of one strand and a carboxyl group of the other strand or of the same strand, respectively, the primary amine group being directly substituted in the 2' position of the strand nucleotide monosaccharide ring, and the carboxyl group being carried by an aliphatic spacer group substituted on a nucleotide or nucleotide analog of the other strand or the same strand, respectively.

The antisense oligodeoxynucleotides and oligonucleotides disclosed in International Application No. WO 92/18522 may also be used. These molecules are stable to degradation and contain at least one transcription control recognition sequence which binds to control proteins and are effective as decoys therefor. These molecules may contain "hairpin" structures, "dumbbell" structures, "modified dumbbell" structures, "cross-linked" decoy structures and "loop" structures.

In another preferred embodiment, the cyclic double-stranded oligonucleotides described in European Patent Application No. 0 572 287 A2 are used. These ligated oligonucleotide "dumbbells" contain the binding site for a transcription factor and inhibit expression of the gene under control of the transcription factor by sequestering the factor.

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Use of the closed antisense oligonucleotides disclosed in International Application No. WO 92/19732 is also contemplated. Because these molecules have no free ends, they are more resistant to degradation by exonucleases than are conventional oligonucleotides. These oligonucleotides may be multifunctional, interacting with several regions which are not adjacent to the target mRNA.

The appropriate level of antisense nucleic acids required to inhibit gene expression may be determined using in vitro expression analysis. The antisense molecule may be introduced into the cells by diffusion, injection, infection or transfection using procedures known in the art. For example, the antisense nucleic acids can be introduced into the body as a bare or naked oligonucleotide, oligonucleotide encapsulated in lipid, oligonucleotide sequence encapsidated by viral protein, or as an oligonucleotide operably linked to a promoter contained in an expression vector. The expression vector may be any of a variety of expression vectors known in the art, including retroviral or viral vectors, vectors capable of extrachromosomal replication, or integrating vectors. The vectors may be DNA or RNA.

The antisense molecules are introduced onto cell samples at a number of different concentrations preferably between 1x10⁻¹⁰M to 1x10⁻⁴M. Once the minimum concentration that can adequately control gene expression is identified, the optimized dose is translated into a dosage suitable for use in vivo. For example, an inhibiting concentration in culture of 1x10⁻⁷ translates into a dose of approximately 0.6 mg/kg bodyweight. Levels of oligonucleotide approaching 100 mg/kg bodyweight or higher may be possible after testing the toxicity of the oligonucleotide in laboratory animals. It is additionally contemplated that cells from the vertebrate are removed, treated with the antisense oligonucleotide, and reintroduced into the vertebrate.

It is further contemplated that the antisense oligonucleotide sequence is incorporated into a ribozyme sequence to enable the antisense to specifically bind and cleave its target mRNA. For technical applications of ribozyme and antisense oligonucleotides see Rossi et al., supra.

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In a preferred application of this invention, the polypeptide encoded by the gene is first identified, so that the effectiveness of antisense inhibition on translation can be monitored using techniques that include but are not limited to antibody-mediated tests such as RIAs and ELISA, functional assays, or radiolabeling.

The extended cDNAs of the present invention (or genomic DNAs obtainable therefrom) may also be used in gene therapy approaches based on intracellular triple helix formation. Triple helix oligonucleotides are used to inhibit transcription from a genome. They are particularly useful for studying alterations in cell activity as it is associated with a particular gene. The extended cDNAs (or genomic DNAs obtainable therefrom) of the present invention or, more preferably, a portion of those sequences, can be used to inhibit gene expression in individuals having diseases associated with expression of a particular gene. Similarly, a portion of the extended cDNA (or genomic DNA obtainable therefrom) can be used to study the effect of inhibiting transcription of a particular gene within a cell. Traditionally, homopurine sequences were considered the most useful for triple helix strategies. However, homopyrimidine sequences can also inhibit gene expression. Such homopyrimidine oligonucleotides bind to the major groove at homopurine:homopyrimidine sequences. Thus, both types of sequences from the extended cDNA or from the gene corresponding to the extended cDNA are contemplated within the scope of this invention.

EXAMPLE 60

Preparation and use of Triple Helix Probes

The sequences of the extended cDNAs (or genomic DNAs obtainable therefrom) are scanned to identify 10-mer to 20-mer homopyrimidine or homopurine stretches which could be used in triple-helix based strategies for inhibiting gene expression. Following identification of candidate homopyrimidine or homopurine stretches, their efficiency in inhibiting gene expression is assessed by introducing varying amounts of oligonucleotides containing the candidate sequences into tissue culture cells which normally express the target gene. The oligonucleotides may be prepared on an oligonucleotide synthesizer or they may be purchased commercially from a company specializing in custom oligonucleotide synthesis, such as GENSET, Paris, France.

The oligonucleotides may be introduced into the cells using a variety of methods known to those skilled in the art, including but not limited to calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection or native uptake.

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Treated cells are monitored for altered cell function or reduced gene expression using techniques such as

Northern blotting, RNase protection assays, or PCR based strategies to monitor the transcription levels of the target
gene in cells which have been treated with the oligonucleotide. The cell functions to be monitored are predicted based
upon the homologies of the target gene corresponding to the extended cDNA from which the oligonucleotide was derived
with known gene sequences that have been associated with a particular function. The cell functions can also be

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predicted based on the presence of abnormal physiologies within cells derived from individuals with a particular inherited disease, particularly when the extended cDNA is associated with the disease using techniques described in Example 53.

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The oligonucleotides which are effective in inhibiting gene expression in tissue culture cells may then be introduced in vivo using the techniques described above and in Example 59 at a dosage calculated based on the in vitro 5 results, as described in Example 59.

In some embodiments, the natural (beta) anomers of the oligonucleotide units can be replaced with alpha anomers to render the oligonucleotide more resistant to nucleases. Further, an intercalating agent such as ethidium bromide, or the like, can be attached to the 3' end of the alpha oligonucleotide to stabilize the triple helix. For information on the generation of oligonucleotides suitable for triple helix formation see Griffin et al. (Science 245:967-10 971 (1989).

EXAMPLE 61

Use of Extended cDNAs to Express an Encoded Protein in a Host Organism

The extended cDNAs of the present invention may also be used to express an encoded protein in a host organism to produce a beneficial effect. In such procedures, the encoded protein may be transiently expressed in the 15 host organism or stably expressed in the host organism. The encoded protein may have any of the activities described above. The encoded protein may be a protein which the host organism lacks or, alternatively, the encoded protein may augment the existing levels of the protein in the host organism.

A full length extended cDNA encoding the signal peptide and the mature protein, or an extended cDNA encoding only the mature protein is introduced into the host organism. The extended cDNA may be introduced into the host 20 organism using a variety of techniques known to those of skill in the art. For example, the extended cDNA may be injected into the host organism as naked DNA such that the encoded protein is expressed in the host organism, thereby producing a beneficial effect.

Alternatively, the extended cDNA may be cloned into an expression vector downstream of a promoter which is active in the host organism. The expression vector may be any of the expression vectors designed for use in gene 25 therapy, including viral or retroviral vectors.

The expression vector may be directly introduced into the host organism such that the encoded protein is expressed in the host organism to produce a beneficial effect. In another approach, the expression vector may be introduced into cells in vitro. Cells containing the expression vector are thereafter selected and introduced into the host organism, where they express the encoded protein to produce a beneficial effect.

EXAMPLE 62

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Use Of Signal Peptides Encoded By 5' Ests Or Sequences Obtained Therefrom To Import Proteins Into Cells

The short core hydrophobic region (h) of signal peptides encoded by the 5'ESTS or extended cDNAs derived from the 5'ESTs of the present invention may also be used as a carrier to import a peptide or a protein of interest, so-

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called cargo, into tissue culture cells (Lin et al., J. Biol. Chem., 270: 14225-14258 (1995); Du et al., J. Peptide Res., 51: 235-243 (1998); Rojas et al., Nature Biotech., 16: 370-375 (1998)).

When cell permeable peptides of limited size (approximately up to 25 amino acids) are to be translocated across cell membrane, chemical synthesis may be used in order to add the hiregion to either the C-terminus or the N-terminus to the cargo peptide of interest. Alternatively, when longer peptides or proteins are to be imported into cells, nucleic acids can be genetically engineered, using techniques familiar to those skilled in the art, in order to link the extended cDNA sequence encoding the hiregion to the 5' or the 3' end of a DNA sequence coding for a cargo polypeptide. Such genetically engineered nucleic acids are then translated either *in vitro* or *in vivo* after transfection into appropriate cells, using conventional techniques to produce the resulting cell permeable polypeptide. Suitable hosts cells are then simply incubated with the cell permeable polypeptide which is then translocated across the membrane.

This method may be applied to study diverse intracellular functions and cellular processes. For instance, it has been used to probe functionally relevant domains of intracellular proteins and to examine protein-protein interactions involved in signal transduction pathways (Lin et al., supra; Lin et al., J. Biol. Chem., 271: 5305-5308 (1996); Rojas et al., J. Biol. Chem., 271: 27456-27461 (1996); Liu et al., Proc. Natl. Acad. Sci. USA, 93: 11819-11824 (1996); Rojas et al., Bioch. Biophys. Res. Commun., 234: 675-680 (1997)).

Such techniques may be used in cellular therapy to import proteins producing therapeutic effects. For instance, cells isolated from a patient may be treated with imported therapeutic proteins and then re-introduced into the host organism.

Alternatively, the h region of signal peptides of the present invention could be used in combination with a nuclear localization signal to deliver nucleic acids into cell nucleus. Such oligonucleotides may be antisense oligonucleotides or oligonucleotides designed to form triple helixes, as described in examples 59 and 60 respectively, in order to inhibit processing and maturation of a target cellular RNA.

EXAMPLE 63

Reassembling & Resequencing of Clones

Full length cDNA clones obtained by the procedure described in Example 27 were double-sequenced. These sequences were assembled and the resulting consensus sequences were then reanalyzed. Open reading frames were reassigned following essentially the same process as the one described in Example 27.

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After this reanalysis process a few abnormalities were revealed. The sequences presented in SEQ ID NOs: 47, 73, 79, 89, 91, 96, 126, 128, 134, and 139 are apparently unlikely to be genuine full length cDNAs. These clones are missing a stop codon and are thus more probably 3' truncated cDNA sequences. Similarly, the sequences presented in SEQ ID NOs: 45, 50, 54, 57, 73, 74, 89, 92, 95, 98, 126, 129, 130, 131 and 139 may also not be genuine full length cDNAs based on homology studies with existing protein sequences. Although both of these sequences encode a potential start methionine each could represent a 5' truncated cDNA.

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In addition, SEQ ID NO: 115 was found to be an alternatively spliced transcript and the identities of some of the bases in SEQ ID NO: 131 were corrected.

Finally, after the reassignment of open reading frames for the clones, new open reading frames were chosen in some instances. For example, in the case of SEO ID NOs: 41, 47, 50, 52, 54-56, 58, 59, 61, 74, 75, 79, 84, 89, 91, 92, 96, 98, 103, 105, 106, 126, 129, 131, and 133 the new open reading frames were no longer predicted to contain a signal peptide.

As discussed above, Table IV provides the sequence identification numbers of the extended cDNAs of the present invention, the locations of the full coding sequences in SEQ ID NOs: 40-140 and 242-377 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the signal peptides (listed under the heading SigPep Location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of stop codons (listed under the heading Stop Codon Location in Table IV) the locations in SEQ ID NOs: 40-140 and 242-377 of polyA signals (listed under the heading g PolyA Signal Location in Table IV) and the locations of polyA sites (listed under the heading PolyA Site Location in Table IV).

As discussed above, Table V lists the sequence identification numbers of the polypeptides of SEQ ID NOs: 141-241 and 378-513, the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the full length polypeptide (second column), the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the signal peptides (third column), and the locations of the amino acid residues of SEQ ID NOs: 141-241 and 379-513 in the mature polypeptide created by cleaving the signal peptide from the fall length polypeptide (fourth column). In Table V, and in the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1 and the first amino acid of the signal peptide is designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

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EXAMPLE 64

Functional Analysis of Predicted Protein Sequences

Following double-sequencing, new contigs were assembled for each of the extended cDNAs of the present invention and each was compared to known sequences available at the time of filing. These sequences originate from the following databases: Genbank (release 108 and daily releases up to October, 15, 1998), Genseq (release 32) PIR (release 33) and SwissProt (release 35). The predicted proteins of the present invention matching known proteins were further classified into 3 categories depending on the level of homology.

The first category contains proteins of the present invention exhibiting more than 70% identical amino acid residues on the whole length of the matched protein. They are clearly close homologues which most probably have the same function or a very similar function as the matched protein.

The second category contains proteins of the present invention exhibiting more remote homologies (40 to 70% over the whole protein) indicating that the protein of the present inventionmay have functions similar to those of the homologous protein.

The third category contains proteins exhibiting homology (90 to 100%) to a domain of a known protein indicating that the matched protein and the protein of the invention may share similar features.

It should be noted that the numbering of amino acids in the protein sequences discussed in Figures 10 to 15, and Table VIII, the first methionine encountered is designated as amino acid number 1. In the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1, and the first amino acid of the signal peptide is designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

In addition all of the corrected amino acid sequences (SEQ ED NOs: 141-241 and 378-513) were scanned for the presence of known protein signatures and motifs. This search was performed against the Prosite 15.0 database, using the Proscan software from the GCG package- Functional signatures and their locations are indicated in Table VIII.

15 A) Proteins which are closely related to known proteins

Protein of SEQ ID NO: 217

The protein of SEQ ID NO: 217 encoded by the extended cDNA SEQ ID NO: 116 isolated from lymphocyte shows complete identity to a human protein TFAR19 that may play a role in apoptosis (Genbank accession number AF014955, SEQ ID NO: 516) as shown by the alignment in figure 10.

Taken together, these data suggest that the protein of SEQ ID NO: 217 may be involved in the control of development and homeostasis. Thus, this protein may be useful in diagnosis and/or treating several types of disorders including, but not limited to, cancer, autoimmune disorders, viral infections such as AIDS, neurodegenerative disorders, osteoporosis.

25 Proteins of SEO ID NOs: 174, 175 and 232

The proteins of SEQ ID NOs: 174, 175 and 232 encoded by the extended cDNAs SEQ ID NOs:. 73, 74 and 131 respectively and isolated from lymphocytes shows complete extensive homologies to a human secreted protein (Genseq accession number W36955, SEQ ID NO: 517). As shown by the alignments of figure 11, the amino acid residues are identical to those of the 110 amino acid long matched protein except for positions 51 and 108-110 of the matched protein for the protein of SEQ ID NOs: 174, for positions 48, 94 and 108-110 of the matched protein of SEQ ID NOs:175 and for positions 94, and 108-110 of the matched protein for the protein of SEQ ID NOs: 232. Proteins of SEQ ID NOs: 174 and 232 may represent alternative forms issued from alternative use of polyadenylation signals.

Taken together, these data suggest that the proteins of SEQ ID NOs: 174, 175 and 232 may play a role in cell proliferation and/or differentiation, in immune responses and/or in haematopoeisis. Thus, this protein or part therein,

may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents and/or to suppress graft rejection.

5 Proteins of SEQ ID NO: 231

The protein of SEQ ID NO: 231 encoded by the extended cDNA SEQ ID NO: 130 shows extensive homology with the human E25 protein (Genbank accession number AFO38953, SEQ ID NO: 515). As shown by the alignments in figure 12, the amino acid residues are identical except for position 159 in the 263 amino acid long matched sequence. The matched protein might be involved in the development and differentiation of haematopoietic stem/progenitor cells.

10 In addition, it is the human homologue of a murine protein thought to be involved in chondro-osteogenic differentiation and belonging to a novel multigene family of integral membrane proteins (Deleersnijder et al, J. Biol. Chem., 271: 19475-19482 (1996)).

The protein of invention contains two short segments from positions 1 to 21 and from 100 to 120 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10 : 685-686 (1994)). The first transmembrane domains matches exactly those predicted for the murine E25 protein.

Taken together, these data suggest that the protein of SEQ ID NO: 231 may be involved in cellular proliferation and differentiation. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer and embryogenesis disorders.

20 Protein of SEO ID NO: 196

The protein of SEQ ID NO: 196 encoded by the extended cDNA SEQ ID NO: 95 shows extensive homology with the human seventransmembrane protein (Genbank accession number Y11395, SEQ ID NO: 518) and its murine homologue (Genbank accession number Y11550). As shown by the alignments in figure 13, the amino acid residues are identical except for position 174 in the 399 amino acid long human matched sequence. The matched protein potentially associated to stomatin may act as a G-protein coupled receptor and is likely to be important for the signal transduction in neurons and haematopoietic cells (Mayer et al, Biochem. Biophys. Acta., 1395: 301-308 (1998)).

Taken together, these data suggest that the protein of SEQ ID NOs: 196 may be involved in signal transduction. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases cardiovascular disorders, hypertension, renal injury and repair and septic shock.

Protein of SEQ ID NO: 158

The protein of SEQ ID NOs: 158 encoded by the extended cDNA SEQ ID NO: 57 shows homology with the murine subunit 7a of the COP9 complex (Genbank accession number AFO71316, SEQ ID NO: 520). As shown by the

alignments in figure 14, the amino acid residues are identical except for positions 90, 172 and 247 in the 275 amino acid long matched sequence. This complex is highly conserved between mammals and higher plants where it has been shown to act as a repressor of photomorphogenesis All the components of the mammalian COP9 complex contain structural features also present in components of the proteasome regulatory complex and the translation initiation complex elF3 complex, suggesting that the mammalian COP9 complex is an important cellular regulator modulating multiple signaling pathways (Wei et al, Curr. Biol., 8: 919-922 (1998)).

Taken together, these data suggest that the protein of SEQ ID NO: 158 may be involved in cellular signaling, probably as a subunit of the human COP9 complex. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair and septic shock.

Protein of SEQ ID NO: 226

The protein of SEQ ID NO: 226 encoded by the extended cDNA SEQ ID NO: 125 shows homology with the bovine subunit B14.5B of the NADH-ubiquinone oxidureductase complex (Arizmendi et al, FEBS Lett., 313: 80-84 (1992) and Swissprot accession -number Q02827, SEQ ID NO: 514). As shown by the alignments in figure 15, the amino acid residues are identical except for positions 3-4, 6-12, 32-34, 47, 53-55, 67 and 69-74 in the 120 amino acid long matched sequence. This complex is the first of four complexes located in the inner mitochondrial membrane and composing the mitochondrial electron transport chain. Complex I is involved in the dehydrogenation of NADH and the transportation of electrons to coenzyme Q. It is composed of 7 subunits encoded by the mitochondrial genome and 34 subunits encoded by the nuclear genome. It is also thought to play a role in the regulation of apoptosis and necrosis. Mitochondriocytopathies due to complex I deficiency are frequently encountered and affect tissues with a high energy demand such as brain (mental retardation, convulsions, movement disorders), heart (cardiomyopathy, conduction disorders), kidney (Fanconi syndrome), skeletal muscle (exercise intolerance, muscle weakness, hypotonia) and/or eye (opthmaloplegia, ptosis, cataract and retinopathy). For a review on complex I see Smeitink et al., Hum. Mol. Gent., 7: 1573-1579 (1998).

Taken together, these data suggest that the protein of SEQ ID NO: 226 may be part of the mitochondrial energy-generating system, probably as a subunit of the NADH-ubiquinone oxidoreductase complex. Thus, this protein or part therein, may be useful in diagnosing and/or treating several disorders including, but not limited to, brain disorders (mental retardation, convulsions, movement disorders), 'heart disorders (cardiomyopathy, conduction disorders), kidney disorders (Fanconi syndrome), skeletal muscle disorders (exercise intolerance, muscle weakness, hypotonia) and/or eye disorders opthmalmoplegia, ptosis, cataract and retinopathy).

B) Proteins which are remotely related to proteins with known functions Proteins of SEQ ID NOs: 149, 150 and 211 The proteins of SEQ ID NOs: 1.49,150 and 211 encoded by the extended cDNAs SEQ ID NOs: 48, 49 and 110 respectively and found in, skeletal muscle shows homologies with T1/ST2 ligand polypeptide of either human (Genbank accession number U41804 and Genseq accession number W09639) or rodent species (Genbank accession number U41805 and Genseq accession number W09640). These polypeptides are thought to be cytokines that bind to the ST2 receptor, a member of the immunoglobulin family homologous to the interleukin-1 receptor and present on some lymphoma cells. They are predicted to be cell-surface proteins containing a short transmembrane domain. (Gayle et al, J. Biol. Chem., 271: 5784-5789 (1996)). Proteins of SEQ ID NOs: 149, 150 and 211 may represent alternative forms issued from alternative use of polyadenylation signals.

The protein of invention contains two short transmembrane segments from positions 5 to 25 and from 195 to 215 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10:685-686 (1994)). The second transmembrane domain matches exactly those of the matched cell-surface protein.

Taken together, these data suggest that the protein of SEQ ID NOs: 149, 150 and 211 may act as a cytokine, thus may play a role in the regulation of cell growth and differentiation and/or in the regulation of the immune response.

Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents such as HIV and/or to suppress graft rejection.

Protein of SEQ ID NO: 177

The protein SEQ ID NO: 177 found in testis encoded by the extended cDNA SEQ ID NO: 76 shows homologies to serine protease inhibitor proteins belonging to the pancreatic trypsin inhibitor family (Kunitz) such as the extracellular proteinase inhibitor named chelonianin (Swissprot accession number P00993). The characteristic PROSITE signature of this family is conserved in the protein of the invention (positions 69 to 87) except for a drastic change of the last cysteine residue into an arginine residue.

Taken together, these data suggest that the protein of SEQ ID NO: 177 may be a protease inhibitor, probably of the Kunitz family. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including but not limited to, cancer and neurodegenerative disorders such as Alzheimer's disease.

Protein of SEO ID NO: 146

The protein SEQ ID NO: 146 encoded by the extended cDNA SEQ ID NO: 45 shows homology to human apolipoprotein L (Genbank accession number AFO19225). The matched protein is a secreted high density lipoprotein associated with apoA-I-containing lipoproteins which play a key role in reverse cholesterol transport.

Taken together, these data suggest that the protein of SEQ ID NO. 146 may play a role in lipid metabolism. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to,

hyperlipidemia, hypercholesterolemia, atherosclerosis, cardiovascular disorders such as, coronary heart disease, and neurodegenerative disorders such as Alzheimer's disease or dementia.

Protein of SEQ ID NO: 163

The protein SEQ ED NO: 163 encoded by the extended cDNA SEQ ID NO: 62 shows homology to the yeast autophagocytosis protein AUT1 (SwissProt accession number P40344). The matched protein is required for starvation-induced non-specific bulk transport of cytoplasmic proteins to the vacuole.

Taken together, these data suggest that the protein of SEQ ID NO: 163 may play a role in protein transport.

Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, autoimmune disorders and immune disorders due to dysfunction of antigen presentation.

C) Proteins homologous to a domain of a protein with known function

Protein of SEQ ID NO: 214

The protein of SEQ ID NO: 214 encoded by the extended cDNA SEQ ID NO: 113 and expressed in adult brain shows extensive homology to part of the murine SHYC protein (Genbank accession number AF072697) which is expressed in the developing and embryonic nervous system as well as along the olfactory pathway in adult brains (Köster et al., Neuroscience Letters., 252: 69-71 (1998)).

Taken together, these data suggest that the protein of SEQ ID NO: 214 may play a role in nervous system development and function. Thus, this protein may be useful in diagnosing and/or treating cancer and/or brain disorders, including neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.

Protein of SEQ ID NO: 225

The protein of SEQ ID NO: 225 encoded by the extended cDNA SEQ ID NO: 124 and expressed in adult prostate belong to the phosphatidylethanolainin-binding protein from which it exhibits the characteristic PROSITE signature from positions 90 to 112 (see table VIII). Proteins from this widespread family, from nematodes to fly, yeast, rodent and primate species, bind hydrophobic ligands such as phospholipids and nucleotides. They are mostly expressed in brain and in testis and are thought to play a role in cell growth and/or maturation, in regulation of the sperm maturation, motility and 'in membrane remodeling. They may act either through signal transduction or through oxidoreduction reactions (for a review see Schoentgen and Jollès, FEBS Letters, 369 : 22-26 (1995)).

Taken together, these data suggest that the protein of SEQ ID NO: 225 may play a role in cell. Thus, these growth, maturation and in membrane remodeling and/or may be related to male fertility. Thus, this protein may be useful in diagnosing and/or treating cancer, neurodegenerative diseases, and/of, disorders related to male fertility and sterility.

Protein of SEO ID NO: 153

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The protein of SEQ ID NO: 153 encoded by the extended cDNA SEQ ID NO. 52 and expressed in brain exhibits homology to different integral membrane proteins. These membrane proteins include the nematode protein SRE-2 (Swissprot accession number Q09273) that belongs to the multigene SRE family of *C. elegans* receptor-like proteins and a family of tricarboxylate carriers conserved between flies and mammals. One member of this matched family is the rat tricarboxylate carrier (Genbank accession number S70011), an anion transporter localized in the inner membrane of mitochondria and involved in the biosynthesis of fatty acids and cholesterol. The protein of the invention contains a short transmembrane segments from positions 5 to 25 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10:685-686 (1994)).

Taken together, these data suggest that the protein of SEO ID NO: 153 may play a role in signal transduction
and/or in molecule transport. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, immune disorders, cardiovascular disorders, hypertension, renal injury and repair and septic shock

Protein of SEQ ID NO: 213

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The protein of SEQ ID NO: 213 encoded by the extended cDNA SEQ ID NO: 112 and expressed in brain exhibits homology with part of the tRNA pseudouridine 55 synthase found in *Escherichia Coli* (Swissprot accession number P09171). This bacterial protein belongs to the NAP57/CBF5/TRUB family of nucleolar proteins found in bacteria, yeasts and mammals involved in rRNA or tRNA biosynthesis, ribosomal subunit assembly and/or centromere/mircotubule binding.

Taken together, these data suggest that the protein of SEQ ID NO: 213 may play a role in rRNA or tRNA biogensis and function. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, hearing loss or disorders linked to chromosomal instability such as dyskeratosis.

Protein of SEQ ED NO: 240

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The protein of SEQ ID NO: 240 encoded by the extended cDNA SEQ ID NO: 139 and expressed in brain exhibits homology with a family of eukaryotic cell surface antigens containing 4 transmembrane domains. The PROSITE signature for this family is conserved in the protein of the invention except for a substitution of an alanine residue in place of any of the following hydrophic residues: leucine, valine, isoleucine or methionine (positions 21 to 36).

The protein of the invention contains three short transmembrane segments from positions 6 to 26, 32 to 52 and from 56 to 76 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10: 685-686 (1994)). These transmembrane domains match the last three transmembrane domains of the matched protein family.

Taken together, these data suggest that the protein of SEQ ID NO: 240 may play a role in immunological and/or inflammatory responses, probably as a cell surface antigen. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or

inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents and/or to suppress graft rejection.

Protein of SEO ID NO: 239

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The protein of SEQ ID NO: 239 encoded by the extended cDNA SEQ ID NO: 138 exhibits homology with a conserved region in a family of NA+/H+ exchanger conserved in yeast, nematode and mammals. These cation/proton exchangers are integral membrane proteins with 5 transmembrane segments involved in intracellular pH regulation, maintenance of cell volume, reabsorption of sodium across specialized epithelia, vectorial transport and are also thought to play a role in signal transduction and especially in the induction of cell proliferation and in the induction of apoptosis.

The protein of invention contains four short transmembrane segments from positions 21 to 41, 48 to 68 and from 131 to 151 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10: 685-686 (1994)). The third and fourth transmembrane domains match the fourth and fifth transmembrane segments of the matched family of proteins.

Taken together, these data suggest that the protein of SEQ ID NO: 239 may play a role in membrane

15 permeability and/or in signal transduction. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair, septic shock as well as disorders of membrane permeability such as diarrhea.

Protein of SEQ ID NO: 200

The protein of SEQ ID NO: 200 encoded by the extended cDNA SEQ ED NO: 99 and expressed in brain exhibits extensive homology to the N-terminus of cell division cycle protein 23 (Genbank accession number AF053977) and also to a lesser extent to its homologue in Saccharomyces cerevisiae. The matched protein is required for chromosome segregation and is part of the anaphae-promoting complex necessary for cell cycle progression to mitosis.

Taken together, these data suggest that the protein of SEQ ID NO: 200 may play a role in cellular mitosis.

Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer and leukemia.

Protein of SEQ ID NO: 230

The protein of SEQ ID NO: 230 encoded by the extended cDNA SEQ ID NO: 129 exhibits extensive homology to the C-terminus of the eta subunit of T-complex polypeptide 1 conserved from yeasts to mammals, and even complete identity with the last 54 amino acid residues of the human protein (Genbank accession number AFO26292). The matched protein is a chaperonin which assists the folding of actins and tubulins in eukaryotic cells upon ATP hydrolysis.

Taken together, these data suggest that the protein of SEO ID NO: 230 may play a role in the folding, transport, assembly and degradation of proteins. Thus, this protein may be useful in diagnosing and/or treating several

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types of disorders including, but not limited to, cancer, cardiovascular disorders, immune disorders, neurodegenerative disorders, osteoporosis and arthritis.

Protein of SEQ ED NO: 167

The protein of SEQ ID NO: 167 encoded by the extended cDNA SEQ ID NO: 66 exhibits homology to a monkey pepsinogen A-4 precursor (Swissprot accession number P27678) and to related members of the aspartyl protease family. The matched protein belongs to a family of widely distributed proteolytic enzymes known to exist in vertebrate, fungi, plants, retroviruses and some plant viruses.

Taken together, these data suggest that the protein of SEQ ID NO: 167 may play a role in the degradation of proteins. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, autoimmune disorders and immune disorders due to dysfunction of antigen presentation.

Protein of SEQ ID NO: 179

The protein of SEQ ID NO: 179 encoded by the extended cDNA SEQ ID NO: 78 found in testis exhibits

15 homology to part of mammalian colipase precursors. Colipases are secreted cofactors for pancreatic lipases that allow the lipase to anchor at the water-lipid interface. Colipase plays a crucial role in the intestinal digestion and absorption of dietary fats. The 5 cysteines characteristic for this protein family are conserved in the protein of the invention although the colipase PROSITE signature is not.

Taken together, these data suggest that the protein of SEQ ED NO: 179 may play a role in the lipid metabolism and/or in male fertility. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, hyperlipidemia, hypercholesterolemia, atherosclerosis, cardiovascular disorders such as coronary heart disease, and neurodegenerative disorders such as Alzheimer's disease or dementia, and disorders linked to male fertility.

25 Protein of SEQ ID NO: 227

The protein of SEQ ID NO: 227 encoded by the extended cDNA SEQ ID NO: 126 exhibits extensive homology to the ATP binding region of a whole family of serine/threonine protein kinases belonging to the CDC2/CDC28 subfamily. The PROSITE signature characteristic for this domain is present in the protein of the invention from positions 10 to 34.

Taken together, these data suggest that the protein of SEQ ED NO: 158 may bind ATP, and even be a protein 30 kinase. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair and septic shock.

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Although this invention has been described in terms of certain preferred embodiments, other embodiments which will be apparent to those of ordinary skill in the art in view of the disclosure herein are also within the scope of this invention. Accordingly, the scope of the invention is intended to be defined only by reference to the appended claims.

As discussed above, the extended cDNAs of the present invention or portions thereof can be used for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to 10 compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting: for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination for expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or 15 potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins or polypeptides provided by the present invention can similarly be used in assays to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit 20 another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other 25 protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing 30 such methods include without limitation "Molecular Cloning; A Laboratory Manual", 2d ed., Cole Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology; Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a

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nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

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SEQUENCE LISTING FREE TEXT

The following free text appears in the accompanying Sequence Listing: In vitro transcription product

oligonucleotide

5 promoter

transcription start site

Von Heijne matrix

Score

matinspector prediction

10 name

TABLE I

SEQ ID NO. in Present application	Provisional Application Disclosing Sequence	SEQ ID NO. in provisional application
40	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	51
41	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	72
42	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	52
43	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	78
44	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	73
45	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	41
46	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	67
47	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	82
48	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	80
49	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	81
50	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	53
51	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	54
52	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	195
53	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	44
54	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	46
55	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	68
56	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	48
57	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	55
58	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	49
59	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	50
60	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	97
61	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	51
62	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	69
63	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	49
64	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	199
65	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	53
66	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	57
67	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	54
68	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	55
69	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	58
70	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	59

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71	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	60
72	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	112
73	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	52
74	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	59
75	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	60
76	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	136
77	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	75
78	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	61
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371	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	. 204
372	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	205
373	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	206
374	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	207
375	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	208
376	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	209
377	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	210

TABLE II: Parameters used for each step of EST analysis

	!	Search Charac	teristics	Selection Charac	teristics
Step	Program	Strand	Parameters	Identity (%))	Length (bp)
Miscellaneous	Blastn	both	S-61 X-16	90	17
tRNA	Fasta	both	•	80	60
rRNA	Blastn	both	S=108	80	40
mtRNA	Blastn	both	S-108	80	40
Procaryotic	Blastn	both	S-144	90	40
Fungal	Blastn	both	S=144	90	40
Alu	fasta*	both		70	40
L1	Blastn	both	S-72	70	40
Repeats	Blastn	both	S=72	70	40
Promoters	Blastn	top	S-54 X-16	90	15⊥
Vertebrate	fasta*	both	S-108	90	30
ESTs	Blatsn	both	S-108 X-16	90	30
Proteins	blastxŋ	top	E-0.001	-	÷ •

^{*} use "Quick Fast" Database Scanner

 $[\]pm$ alignment further constrained to begin closer than 10bp to EST\5' end 5 $\,\eta\,$ using BLOSUM62 substitution matrix

TABLE III: Parameters used for each step of extended cDNA analysis

	Search characteristics			Selection characteristics			
Step	Program	Strand	Parameters	Identity (%)	Length (bp)	Comments	
miscellaneous •	FASTA	both		90	15		
tRNA*	FASTA	both		80	90		
rRNA*	BLASTN	both	S-108	80	40		
mtRNA*	BLASTN	both	S-108	80	40		
Procaryotic*	BLASTN	both	S-144	90	40		
Fungal*	BLASTN	both	S-144	90	40		
Alu*	BLASTN	both	S-72	70	40	max 5 matches, masking	
L1 ¹	BLASTN	both	S-72	70	40	max 5 matches, masking	
Repeats*	BLASTN	both	S-72	70	40	masking	
PolyA	BLAST2N	top	W-6,S-10,E-1000	90	8	in the last 20 nucleotides	
Polyadenylati on signal	•	top	AATAAA allowing 1 mis	match		in the 50 nucleotides preceding the 5' end of the polA	
Vertebrate*	BLASTN then FASTA	both		90 then 70	30	first BLASTN and then FASTA on matching sequences	
ESTs*	BLAST2N	both	•	90	30		
Geneseq	BLASTN	both	W-8, B-10	90	30		
ORF	BLASTP	top	W-8, B-10	·	•	on ORF proteins, max 10 matches	
Proteins*	BLASTX	top	E=0.001	70	30		

steps common to EST analysis and using the same algorithms and parameters
 steps also used in EST analysis but with different algorithms and/or parameters

TABLE IV

ld	FCS Location	SigPep Location	Mature	Stop	PolyA Signal	PolyA Site Location
			Polypeptide Location	Codon Location	Location	
40	7 through 471	7 through 99	100 through 471	472	537 through 542	554 through 568
41	168 through 332	1.	168 through 332	333	557 through 562	
42	51 through 251	51 through 110	111 through 251	252	849 through 854	882 through 895
43	20 through 613	20 through 82	83 through 613	614	1.	
44	12 through 416	12 through 86	87 through 416	417	425 through 430	445 through 458
45	276 through 1040	276 through 485	486 through 1040	1041	1.	2024 through 2036
46	443 through 619	443 through 589	590 through 619	620	1.	1267 through 1276
47	206 through 747	1.	206 through 747	1.	1.	
48	36 through 521	36 through 104	105 through 521	522	528 through 533	548 through 561
49	36 through 395	36 through 104	105 through 395	396	599 through 604	619 through 632
50	21 through 41	•	21 through 41	42	328 through 333	357 through 370
51	35 through 631	35 through 160	161 through 631	632	901 through 906	979 through 994
52	271 through 399		271 through 399	400	1.	
53	103 through 252	103 through 213	214 through 252	253		588 through 597
54	2 through 460		2 through 460	461	713 through 718	735 through 748
55	31 through 231	•	31 through 231	232	769 through 774	690 through 703
56	305 through 565		305 through 565	566	694 through 699	713 through 725
57	124 through 873	124 through 378	379 through 873	874	1673 through 1678	1694 through 1705
58	135 through 206		135 through 206	207	850 through 855	1056 through 1069
59	135 through 818	·	135 through 818	819	909 through 914	1071 through 1084
60	33 through 290	33 through 92	93 through 290	291	•	1.
61	485 through 616	·	485 through 616	617		669 through 682
62	54 through 995	54 through 227	228 through 995	996	1130 through 1135	1181 through 1191
63	657 through 923	657 through 896	897 through 923	924	957 through 962	974 through 1008
64	18 through 311	18 through 62	63 through 311	312		
65	151 through 426	151 through 258	259 through 426	427	505 through 510	527 through 538
66	10 through 1062	10 through 57	58 through 1062	1063	1710 through 1715	1735 through 1747
67	78 through 491	78 through 218	219 through 491	492	1652 through 1657	1673 through 1686
68	69 through 371	69 through 287	288 through 371	372	510 through 515	530 through 542
69	2 through 757	2 through 205	206 through 757	758	•	1160 through 1174
70	2 through 1051	2 through 205	206 through 1051	1052	1248 through 1253	1272 through 1285
71	2 through 1171	2 through 205	206 through 1171	1172	1368 through 1373	1386 through 1398
72	42 through 611	42 through 287	288 through 611	612	787 through 792	808 through 821
73	62 through 916	62 through 757	758 through 916			904 through 916
74	62 through 520		62 through 520	521	1124 through 1129	1141 through 1153
75	21 through 167		21 through 167	168	•	
76	22 through 318	22 through 93	94 through 318	319	497 through 502	516 through 526
77	8 through 292	8 through 118	119 through 292	293	317 through 322	339 through 352
78	16 through 378	16 through 84	85 through 378	379	502 through 507	522 through 542

CONT. TABLE IV

CON	IT. TABLE IV					
79	57 through 233	1.	57 through 233	·		•
80	83 through 340	83 through 124	125 through 340	341	573 through 578	607 through 660
81	47 through 541	47 through 220	221 through 541	542	·	597 through 605
82	46 through 285	46 through 150	151 through 285	286	364 through 369	385 through 396
83	22 through 240	22 through 84	85 through 240	241	397 through 402	421 through 432
84	89 through 382	•	89 through 382	383	•	408 through 420
85	80 through 415	80 through 142	143 through 415	416	471 through 476	488 through 501
86	152 through 361	152 through 283	284 through 361	362		
87	32 through 307	32 through 70	71 through 307	308	1240 through 1245	1261 through 1272
88	114 through 734	114 through 239	240 through 734	735	768 through 773	793 through 804
89	199 through 802	·	199 through 802	·	780 through 785	791 through 802
90	38 through 1174	38 through 148	149 through 1174	1175	1452 through 1457	1478 through 1490
91	26 through 361	•	26 through 361		•	350 through 361
92	3 through 131	·	3 through 131	132	•	591 through 605
93	33 through 185	33 through 80	81 through 185	186	570 through 575	586 through 591
94	184 through 915	184 through 237	238 through 915	916	1119 through 1124	1139 through 1150
95	58 through 1116	58 through 159	160 through 1116	1117	1486 through 1491	1504 through 1513
96	327 through 417	·	327 through 417		•	404 through 417
97	63 through 398	63 through 206	207 through 398	399		
98	2 through 163	•	2 through 163	164	488 through 493	511 through 522
99	13 through 465	13 through 75	76 through 465	466	1.	
100	20 through 703	20 through 94	95 through 703	704	1000 through 1005	1023 through 1041
101	103 through 294	103 through 243	244 through 294	295		
102	81 through 518	81 through 173	174 through 518	519		
103	66 through 326		66 through 326	327	1066 through 1071	1087 through 1098
104	170 through 289	170 through 250	251 through 289	290	•	
105	36 through 497		36 through 497	498	650 through 655	663 through 685
106	18 through 320	•	18 through 320	321	539 through 544	542 through 554
107	71 through 1438	71 through 136	137 through 1438	1439	1644 through 1649	1665 through 1678
108	25 through 318	25 through 75	76 through 318	319	452 through 457	482 through 494
109	84 through 332	84 through 170	171 through 332	333	•	702 through 714
110	32 through 718	32 through 100	101 through 718	719	770 through 775	793 through 805
111	26 through 481	26 through 88	89 through 481	482	755 through 760	775 through 787
112	26 through 562	26 through 187	188 through 562	563	·	·
113	4 through 810	4 through 279	280 through 810	811	858 through 863	881 through 893
114	55 through 459	55 through 120	121 through 459	460	1444 through 1449	1462 through 1475
115	48 through 248	48 through 161	162 through 248	249	283 through 288	308 through 321
116	25 through 399	25 through 186	187 through 399	400		
117	10 through 1137	10 through 72	73 through 1137	1138	1144 through 1149	1162 through 1173
118	72 through 704	72 through 161	162 through 704	705	772 through 777	
119	44 through 505	44 through 223	224 through 505	506	•	
120	25 through 393	25 through 150	151 through 393	394	734 through 739	757 through 770

CONT. TABLE IV

- 601	II. TABLE IV					
121	58 through 1095	58 through 114	115 through 1095	1096	•	1202 through 1213
122	31 through 660	31 through 90	91 through 660	661	1288 through 1293	1307 through 1318
123	31 through 582	31 through 90	91 through 582	583	816 through 821	840 through 853
124	15 through 695	15 through 80	81 through 695	696	795 through 800	814 through 826
125	74 through 295	74 through 196	197 through 295	296	545 through 550	561 through 571
126	440 through 659	·	440 through 659	·	601 through 606	
127	38 through 283	38 through 85	86 through 283	284	257 through 262	•
128	121 through 477	121 through 288	289 through 477	1.		
129	2 through 163	·	2 through 163	164	292 through 297	310 through 323
130	46 through 675	46 through 87	88 through 675	676	1364 through 1369	1383 through 1392
131	62 through 385		62 through 385	386	974 through 979	987 through 999
132	422 through 550	422 through 475	476 through 550	551	1.	714 through 725
133	124 through 231		124 through 231	232		387 through 400
134	131 through 1053	131 through 169	170 through 1053	 	1019 through 1024	1.
135	86 through 403	86 through 181	182 through 403	404	1097 through 1102	1117 through 1128
136	37 through 162	37 through 93	94 through 162	163	224 through 229 .	243 through 254
137	31 through 381	31 through 90	91 through 381	382		875 through 886
138	46 through 579	46 through 156	157 through 579	580	 	
139	92 through 471	92 through 172	173 through 471	 . 	454 through 459	458 through 471
140	154 through 675	154 through 498	499 through 675	676	819 through 824	838 through 849
242	18 through 173	18 through 77	78 through 173	174	864 through 869	882 through 893
243	17 through 595	17 through 85	86 through 595	596	820 through 825	840 through 851
244	89 through 334	89 through 130	131 through 334	335	462 through 467	484 through 495
245	21 through 614	21 through 83	84 through 614	615	849 through 854	873 through 884
246	94 through 573	94 through 258	259 through 573	574	862 through 867	886 through 897
247	74 through 397	74 through 127	128 through 397	398	472 through 477	507 through 518
248	51 through 242	51 through 116	117 through 242	243	319 through 324	339 through 350
249	111 through 191	111 through 155	156 through 191	192	965 through 970	986 through 996
250	45 through 602	45 through 107	108 through 602	603	828 through 833	850 through 860
251	24 through 560	24 through 101	102 through 560	561	563 through 568	583 through 593
252	109 through 558	109 through 273	274 through 558	559		1104 through 1114
253	128 through 835	128 through 220	221 through 835	836	1145 through 1150	1170 through 1181
254	59 through 505	59 through 358	359 through 505	506	1042 through 1047	1062 through 1073
255	1 through 207	1 through 147	148 through 207	208	784 through 789	807 through 818
256	12 through 734	12 through 101	102 through 734	.735	914 through 919	
257	378 through 518	378 through 467	468 through 518	519	607 through 612	961 through 971 628 through 640
258	110 through 304	110 through 193	194 through 304	305	708 through 713	
259	201 through 419	201 through 272	273 through 419	420	601 through 606	732 through 743
260	123 through 302	123 through 176	177 through 302	303		627 through 637
261	98 through 673	98 through 376	377 through 673	674	1279 through 1284	1301 through 1312
262	17 through 463	17 through 232	233 through 463	464	657 through 662	1025 through 1035
263	263 through 481	263 through 322	323 through 481	482	657 through 662	684 through 696
		200 111100911 022	023 HAOUGH 401	402	•	858 through 868

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CON	IT. TABLE IV					•
264	42 through 299	42 through 101	102 through 299	300	1	762 through 775
265	198 through 431	198 through 260	261 through 431	432	·	1064 through 1074
266	279 through 473	279 through 362	363 through 473	474	944 through 949	970 through 981
267	12 through 644	12 through 92	93 through 644	645	1002 through 1007	1020 through 1031
268	91 through 459	91 through 330	331 through 459	460	•	1271 through 1281
269	70 through 327	70 through 147	148 through 327	328	1741 through 1746	1763 through 1774
270	12 through 497	12 through 104	105 through 497	498	935 through 940	955 through 967
271	90 through 383	90 through 200	201 through 383	384	609 through 614	632 through 643
272	332 through 541	332 through 376	377 through 541	542	739 through 744	761 through 773
273	43 through 222	43 through 177	178 through 222	223	530 through 535	555 through 566
274	115 through 231	115 through 180	181 through 231	232	419 through 424	445 through 455
275	232 through 384	232 through 300	301 through 384	385	650 through 655	662 through 673
276	143 through 427	143 through 286	287 through 427	428	606 through 611	628 through 639
277	284 through 463	284 through 379	380 through 463	464		762 through 772
278	162 through 671	162 through 398	399 through 671	672	805 through 810	830 through 840
279	63 through 632	63 through 308	309 through 632	633	808 through 813	829 through 840
280	21 through 362	21 through 200	201 through 362	363	821 through 826	838 through 849
281	21 through 503	21 through 344	345 through 503	504	1305 through 1310	1330 through 1341
282	1 through 201	1 through 63	64 through 201	202	637 through 642	660 through 671
283	39 through 1034	39 through 134	135 through 1034	1035	1566 through 1571	1587 through 1597
284	69 through 263	69 through 125	126 through 263	264	1173 through 1178	1196 through 1205
285	115 through 285	115 through 204	205 through 285	286	505 through 510	525 through 536
286	90 through 344	90 through 140	141 through 344	345	500 through 505	515 through 527
287	57 through 311	57 through 107	108 through 311	312	467 through 472	482 through 493
288	96 through 302	96 through 182	183 through 302	303	1.	501 through 514
289	161 through 526	161 through 328	329 through 526	527		799 through 811
290	210 through 332	210 through 299	300 through 332	333	594 through 599	613 through 625
291	212 through 361	212 through 319	320 through 361	362	650 through 655	673 through 684
292	75 through 482	75 through 128	129 through 482	483	595 through 600	618 through 627
293	50 through 631	50 through 244	245 through 631	632	777 through 782	801 through 812
294	154 through 576	154 through 360	361 through 576	577	737 through 742	763 through 775
295	154 through 897	154 through 360	361 through 897	898	1017 through 1022	1044 through 1054
296	146 through 292	146 through 253	254 through 292	293	395 through 400	433 through 444
297	126 through 383	126 through 167	168 through 383	384	726 through 731	743 through 754
298	66 through 497	66 through 239	240 through 497	498	594 through 599	618 through 629
299	49 through 411	49 through 96	97 through 411	412	732 through 737	750 through 763
300	49 through 534	49 through 96	97 through 534	535	593 through 598	612 through 623
301	86 through 415	86 through 145	146 through 415	416	540 through 545	560 through 571
302	56 through 268	56 through 100	101 through 268	269	584 through 589	601 through 612
303	32 through 328	32 through 103	104 through 328	329	508 through 513	528 through 539
304	21 through 527	21 through 95	96 through 527	528	921 through 926	953 through 963
305	147 through 647	147 through 374	375 through 647	648		668 through 681
					I	

CONT. TABLE IV

CO	NT. TABLE IV					
306	262 through 471	262 through 306	307 through 471	472	663 through 668	682 through 693
307	74 through 1216	74 through 172	173 through 1216	1217	1627 through 1632	1640 through 1652
308	48 through 164	48 through 89	90 through 164	165	482 through 487	505 through 517
309	185 through 334	185 through 295	296 through 334	335	355 through 360	392 through 405
310	195 through 347	195 through 272	273 through 347	348	1037 through 1042	1071 through 1082
311	90 through 815	90 through 179	180 through 815	816	883 through 888	905 through 916
312	52 through 513	52 through 231	232 through 513	514	553 through 558	572 through 583
313	172 through 438	172 through 354	355 through 438	439	682 through 687	685 through 697
314	148 through 366	148 through 225	226 through 366	367	770 through 775	792 through 803
315	175 through 336	175 through 276	277 through 336	337	-	812 through 823
316	191 through 553	191 through 304	305 through 553	554	766 through 771	804 through 817
317	106 through 603	106 through 216	217 through 603	604		1102 through 1112
318	47 through 586	47 through 124	125 through 586	587	1583 through 1588	1614 through 1623
319	99 through 371	99 through 290	291 through 371	372	491 through 496	513 through 524
320	44 through 814	44 through 112	113 through 814	815		978 through 989
321	3 through 581	3 through 182	183 through 581	582	·	1006 through 1016
322	107 through 427	107 through 190	191 through 427	428	499 through 504	516 through 529
323	45 through 407	45 through 83	84 through 407	408	1008 through 1013	1032 through 1042
324	201 through 332	201 through 251	252 through 332	333		869 through 880
325	217 through 543	217 through 255	256 through 543	544		1206 through 1217
326	18 through 446	18 through 140	141 through 446	447	930 through 935	948 through 959
327	29 through 724	29 through 118	119 through 724	725	886 through 891	910 through 920
328	404 through 586	404 through 466	467 through 586	587	1304 through 1309	1334 through 1344
329	331 through 432	331 through 387	388 through 432	433	548 through 553	573 through 585
330	59 through 703	59 through 220	221 through 703	704	886 through 891	903 through 914
331	672 through 752	672 through 722	723 through 752	753		1150 through 1161
332	57 through 311	57 through 128	129 through 311	312	332 through 337	351 through 363
333	80 through 232	80 through 127	128 through 232	233	617 through 622	634 through 645
334	91 through 291	91 through 219	220 through 291	292	367 through 372	389 through 400
335	196 through 384	196 through 240	241 through 384	385	461 through 466	485 through 496
336	54 through 590	54 through 227	228 through 590	591		955 through 965
337	133 through 846	133 through 345	346 through 846	847		890 through 901
338	138 through 671	138 through 248	249 through 671	672	1319 through 1324	1338 through 1347
339	124 through 411	124 through 186	187 through 411	412	948 through 953	971 through 983
340	372 through 494	372 through 443	444 through 494	495	708 through 713	732 through 745
341	112 through 450	112 through 192	193 through 450	451	1053 through 1058	1095 through 1106
342	117 through 866	117 through 170	171 through 866	867	1159 through 1164	1178 through 1190
343	13 through 465	13 through 75	76 through 465	466	1035 through 1040	1060 through 1070
344	2 through 718	2 through 76	77 through 718	719	1170 through 1175	1203 through 1213
345	86 through 709	86 through 361	362 through 709	710	943 through 948	963 through 973
346	63 through 320	63 through 179	180 through 320	321	771 through 776	799 through 810
347	299 through 418	299 through 379	380 through 418	419	739 through 744	762 through 771
					<u> </u>	

CONT. TABLE IV

348	186 through 380	186 through 233	234 through 380	381	383 through 388	396 through 409
349	69 through 458	69 through 233	234 through 458	459	564 through 569	602 through 613
350	12 through 638	12 through 263	264 through 638	639	951 through 956	975 through 985
351	282 through 389	282 through 332	333 through 389	390	1413 through 1418	1437 through 1447
352	208 through 339	208 through 294	295 through 339	340	·	1631 through 1641
353	69 through 557	69 through 224	225 through 557	558	849 through 854	870 through 883
354	134 through 325	134 through 274	275 through 325	326		718 through 729
355	78 through 731	78 through 227	228 through 731	732	· · · · · · · · · · · · · · · · · · ·	1002 through 1013
356	46 through 693	46 through 90	91 through 693	694	937 through 942	962 through 973
357	126 through 527	126 through 182	183 through 527	528	834 through 839	856 through 867
358	66 through 320	66 through 113	114 through 320	321	490 through 495	508 through 519
359	73 through 948	73 through 159	160 through 948	949	•	1016 through 1028
360	69 through 434	69 through 236	237 through 434	435	419 through 424	441 through 452
361	628 through 804	628 through 711	712 through 804	805		864 through 875
362	70 through 366	70 through 108	109 through 366	367	496 through 501	521 through 531
363	70 through 366	70 through 108	109 through 366	367	•	1233 through 1244
364	111 through 434	111 through 185	186 through 434	435		618 through 631
365	19 through 567	19 through 63	64 through 567	568	749 through 754	771 through 781
366	19 through 312	19 through 63	64 through 312	313	896 through 901	921 through 931
367	64 through 612	64 through 234	235 through 612	613	1.	839 through 849
368	39 through 458	39 through 80	81 through 458	459	613 through 618	633 through 644
369	9 through 185	9 through 50	51 through 185	186	·	906 through 918
370	14 through 316	14 through 121	122 through 316	317	442 through 447	458 through 471
371	70 through 1092	70 through 234	235 through 1092	1093	1475 through 1480	1493 through 1504
372	274 through 597	274 through 399	400 through 597	598	731 through 736	754 through 765
373	230 through 469	230 through 307	308 through 469	470	1004 through 1009	1027 through 1040
374	72 through 545	72 through 203	204 through 545	546		1151 through 1162
375	36 through 425	36 through 119	120 through 425	426	1215 through 1220	1240 through 1250
376	155 through 751	155 through 340	341 through 751	752	912 through 917	937 through 947
377	46 through 585	46 through 120	121 through 585	586	584 through 589	606 through 619

TABLE V

		I ABLE V	
ld	Full Length Polypeptide Location	Signal Peptide Location	Mature Polypeptide Location
141	-31 through 124	-31 through -1	1 through 124
142	1 through 55		1 through 55
143	-20 through 47	-20 through -1	1 through 47
144	-21 through 177	-21 through -1	1 through 177
145	-25 through 110	-25 through -1	1 through 110
146	-70 through 185	-70 through -1	1 through 185
147	-49 through 10	-49 through -1	1 through 10
148	1 through 180		1 through 180
149	-23 through 139	-23 through -1	1 through 139
150	-23 through 97	-23 through -1	1 through 97
151	1 through 7		
152	-42 through 157	-42 through -1	1 through 7
153	1 through 43	TZ till dagit -1	1 through 157
154	-37 through 13	-37 through -1	1 through 43
155	1 through 153	-07 till bugil -1	1 through 13
156	1 through 67		1 through 153
157	1 through 87	•	1 through 67
158	-85 through 165	-85 through -1	1 through 87
159	1 through 24		1 through 165
160	1 through 228	·	1 through 24
161	-20 through 66	20 45	1 through 228
162	1 through 44	-20 through -1	1 through 66
163	-58 through 256		1 through 44
164	-80 through 9	-58 through -1	1 through 256
165	-15 through 83	-80 through -1	1 through 9
166	-36 through 56	-15 through -1	1 through 83
167	-16 through 335	-36 through -1	1 through 56
168	-47 through 91	-16 through -1	1 through 335
169	-73 through 28	-47 through -1	1 through 91
170	-68 through 184	-73 through -1	1 through 28
171	-68 through 282	-68 through -1	1 through 184
172	-68 through 322	-68 through -1	1 through 282
173	-82 through 108	-68 through -1	1 through 322
174	-232 through 53	-82 through -1	1 through 108
175	1 through 153	-232 through -1	1 through 53
176	1 through 49		1 through 153
177			1 through 49
178	-24 through 75	-24 through -1	1 through 75
179	-37 through 58 -23 through 98	-37 through -1	1 through 58
180	1 through 59	-23 through -1	1 through 98
181	-14 through 72	•	1 through 59
182		-14 through -1	1 through 72
183	-58 through 107	-58 through -1	1 through 107
184	-35 through 45	-35 through -1	1 through 45
185	-21 through 52	-21 through -1	1 through 52
186	1 through 98		1 through 98
187	-21 through 91	-21 through -1	1 through 91
188	-44 through 26	-44 through -1	1 through 26
189	-13 through 79	-13 through -1	1 through 79
190	-42 through 165	-42 through -1	1 through 165
100	1 through 201		1 through 201

CONT. TABLE V

CUNT. TAB	SEE V		• • • • • • • • • • • • • • • • • • • •
191	-37 through 342	-37 through -1	1 through 342
192	1 through 112	·	1 through 112
193	1 through 43	•	1 through 43
194	-16 through 35	-16 through -1	1 through 35
195	-18 through 226	-18 through -1	1 through 226
196	-34 through 319	-34 through -1	1 through 319
197	1 through 30		1 through 30
198	-48 through 64	-48 through -1	1 through 64
199	1 through 54		1 through 54
200	-21 through 130	-21 through -1	1 through 130
201	-25 through 203	-25 through -1	1 through 203
202	-47 through 17	-47 through -1	1 through 17
203	-31 through 115	-31 through -1	1 through 115
204	1 through 87		1 through 87
205	-27 through 13	-27 through -1	1 through 13
206	1 through 154		1 through 154
207	1 through 101	·	
208	-22 through 434	-22 through -1	1 through 101
209	-17 through 81	-17 through -1	1 through 434
210	-29 through 54	-29 through -1	1 through 81
211	-23 through 206	-23 through -1	1 through 54
212	-21 through 131	-21 through -1	1 through 206
213	-54 through 125	-54 through -1	1 through 131
214	-92 through 177	-92 through -1	1 through 125
215	-22 through 113	-22 through -1	1 through 177
216	-38 through 29	-38 through -1	1 through 113
217	-54 through 71	-54 through -1	1 through 29
218	-21 through 355	-21 through -1	1 through 71
219	-30 through 181	-30 through -1	1 through 355
220	-60 through 94	-60 through -1	1 through 181
221	-42 through 81	-42 through -1	1 through 94
222	-19 through 327	-19 through -1	1 through 81
223	-20 through 190	-20 through -1	1 through 327
224	-20 through 164	-20 through -1	1 through 190
225	-22 through 205	-22 through -1	1 through 164
226	-41 through 33	-41 through -1	1 through 205
227	1 through 73	-47 tinoagn -1	1 through 33
228	-16 through 66	-16 through -1	1 through 73
229	-56 through 63	-56 through -1	1 through 66
230	1 through 54	-30 through -1	1 through 63
231	-14 through 196	14 through 1	1 through 54
232	1 through 108	-14 through -1	1 through 196
233	-18 through 25	10 shows 1	1 through 108
234	1 through 36	-18 through -1	1 through 25
235	-13 through 294	12 through 1	1 through 36
236	-32 through 74	-13 through -1	1 through 294
237	-19 through 23	-32 through -1	1 through 74
238	·20 through 97	-19 through -1	1 through 23
239	-37 through 141	-20 through -1	1 through 97
240	-27 through 99	-37 through -1	1 through 141
241	-115 through 59	-27 through -1	1 through 99
378	-20 through 32	-115 through -1	1 through 59
379	-20 through 32	-20 through -1	1 through 32
380	-14 through 68	-23 through -1	1 through 170
	- 14 through 66	-14 through -1	1 through 68

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CONT. TABLE V

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CUNT. TABLE	<u>V</u>		•
436	-16 through 105	-16 through -1	1 through 105
437	-16 through 146	-16 through -1	1 through 146
438	-20 through 90	-20 through -1	1 through 90
439	-15 through 56	-15 through -1	1 through 56
440	-24 through 75	-24 through -1	1 through 75
441	-25 through 144	-25 through -1	1 through 144
442	-76 through 91	-76 through -1	1 through 91
443	-15 through 55	-15 through -1	1 through 55
444	-33 through 348	-33 through -1	1 through 348
445	-14 through 25	-14 through -1	1 through 25
446	-37 through 13	-37 through -1	1 through 13
447	-26 through 25	-26 through -1	1 through 25
448	-30 through 212	-30 through -1	1 through 212
449	-60 through 94	-60 through -1	1 through 94
450	-61 through 28	-61 through -1	1 through 28
451	-26 through 47	-26 through -1	1 through 47
452	-34 through 20	-34 through -1	1 through 20
453	-38 through 83	-38 through -1	1 through 83
454	-37 through 129	-37 through -1	1 through 129
455	-26 through 154	-26 through -1	1 through 154
456	-64 through 27	-64 through -1	1 through 27
457	-23 through 234	-23 through -1	1 through 234
458	-60 through 133	-60 through -1	1 through 133
459	-28 through 79	-28 through -1	1 through 79
460	-13 through 108	-13 through -1	1 through 108
461	-17 through 27	-17 through -1	1 through 27
462	-13 through 96	-13 through -1	1 through 96
463	-41 through 102	-41 through -1	1 through 102
464	-30 through 202	-30 through -1	1 through 202
465	-21 through 40	-21 through -1	1 through 40
466	-19 through 15	-19 through -1	1 through 15
467	-54 through 161	-54 through -1	1 through 161
468	-17 through 10	-17 through -1	1 through 10
469	-24 through 61	-24 through -1	1 through 61
470	-16 through 35	-16 through -1	1 through 35
471	-43 through 24	-43 through -1	1 through 24
472	-15 through 48	-15 through -1	1 through 48
473	-58 through 121	-58 through -1	1 through 121
474	-71 through 167	-71 through -1	1 through 167
475	-37 through 141	-37 through -1	1 through 141
476	-21 through 75	-21 through -1	1 through 75
477	-24 through 17	-24 through -1	1 through 17
478	-27 through 86	-27 through -1	1 through 86
479	-18 through 232	-18 through -1	1 through 232
480	-21 through 130	-21 through -1	1 through 130
481	-25 through 214	-25 through -1	1 through 214
482	-92 through 116	-92 through -1	1 through 116
483	-39 through 47	-39 through -1	1 through 47
484	-27 through 13	-27 through -1	1 through 13
485	-16 through 49	-16 through -1	1 through 49
486	-55 through 75	-55 through -1	1 through 75
487	-84 through 125	-84 through -1	1 through 125
488	-17 through 19	-17 through -1	1 through 19
489	-29 through 15	-29 through -1	. 1 through 15

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490	-52 through 111	-52 through -1	1 through 111
491	-47 through 17	-47 through -1	
492	-50 through 168	-50 through -1	1 through 17
493	-15 through 201	-15 through -1	1 through 168
494	-19 through 115	-19 through -1	1 through 201
495	-16 through 69	-16 through -1	1 through 115
496	-29 through 263	-29 through -1	1 through 69
497	-56 through 66	-56 through -1	1 through 263
498	-28 through 31		1 through 66
499	-13 through 86	-28 through -1	1 through 31
500	-13 through 86	-13 through -1	1 through 86
501	-25 through 83	-13 through -1	1 through 86
502	-15 through 168	-25 through -1	1 through 83
503		-15 through -1	1 through 168
504	-15 through 83	-15 through -1	1 through 83
505	-57 through 126	-57 through -1	1 through 126
506	-14 through 126	-14 through -1	1 through 126
	-14 through 45	-14 through -1	1 through 45
507	-36 through 65	-36 through -1	1 through 65
508	-55 through 286	-55 through -1	1 through 286
509	-42 through 66	-42 through -1	1 through 66
510	-26 through 54	-26 through -1	1 through 54
511	-44 through 114	-44 through -1	1 through 114
512	-28 through 102	-28 through -1	1 through 102
513	-62 through 137	-62 through -1	1 through 137
514	-25 through 155	-25 through -1	1 through 155
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TABLE VI

		I ABLE VI
ld	Collection refs	Deposit Name
40	ATCC # 98921	SignalTag 121-144
41	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
42	ATCC # 98921	SignalTag 121-144
43	ATCC # 98920	SignalTag 67-90
44	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
45	ATCC # 98920	SignalTag 67-90
46	ATCC # 98923	SignalTag 44-66
47	ATCC # 98920	SignalTag 67-90
48	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
49	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
50	ATCC # 98921	SignalTag 121-144
51	ATCC # 98921	SignalTag 121-144
52	ATCC # 98920	SignalTag 67-90
53	ATCC # 98923	SignalTag 44-66
54	ATCC # 98920	SignalTag 67-90
55	ATCC # 98920	SignalTag 67-90
56	ATCC # 98920	SignalTag 67-90
57	ATCC # 98921	SignalTag 121-144
58	ATCC # 98920	SignalTag 67-90
59	ATCC # 98920	SignalTag 67-90
50	ATCC # 98920	SignalTag 67-90
31	ATCC # 98923	SignalTag 44-66
2	ATCC # 98923	SignalTag 44-66
3	ATCC # 98923	SignalTag 44-66
4	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
5	ATCC # 98923	SignalTag 44-66
6	ATCC # 98921	SignalTag 121-144
7	ATCC # 98920	SignalTag 67-90
8	ATCC # 98920	SignalTag 67-90
9	ATCC # 98921	SignalTag 121-144
0	ATCC # 98921	SignalTag 121-144
1	ATCC # 98921	SignalTag 121-144
2	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
3	ATCC # 98923	SignalTag 44-66

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74	ATCC # 98923	SignalTag 44-66	-
75	ATCC # 98920	SignalTag 67-90	
76	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
77	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
78	ATCC # 98921	SignalTag 121-144	
79	ATCC # 98923	SignalTag 44-66	
80	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
81	ATCC # 98921	SignalTag 121-144	
82	ATCC # 98920	SignalTag 67-90	
83	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
84	ATCC # 98923	SignalTag 44-66	
85	ATCC # 98923	SignalTag 44-66	
86	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	\neg
87	ATCC # 98923	SignalTag 44-66	
88	ATCC # 98923	SignalTag 44-66	
89	ATCC # 98923	SignalTag 44-66	
90	ATCC # 98923	SignalTag 44-66	
91	ATCC # 98923	SignalTag 44-66	
92	ATCC # 98920	SignalTag 67-90	
93	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
94	ATCC # 98923	SignalTag 44-66	
95	ATCC # 98923	SignalTag 44-66	
96	ATCC # 98920	SignalTag 67-90	
97	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
98	ATCC # 98921	SignalTag 121-144	
99	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
100	ATCC # 98921	SignalTag 121-144	\exists
101	ATCC # 98920	SignalTag 67-90	
102	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
103	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	\neg
104	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	
105	ATCC # 98921	SignalTag 121-144	
06	ATCC # 98920	SignalTag 67-90	
107	ATCC # 98920	SignalTag 67-90	\dashv
801	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	\dashv
09	ATCC # 98923	SignalTag 44-66	
10	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120	\dashv

111	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120.
112	ATCC # 98920	SignalTag 67-90
113	ATCC # 98920	SignalTag 67-90
114	ATCC # 98923	SignalTag 44-66
115	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
116	ATCC # 98920	SignalTag 67-90
117	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
118	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
119	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
120	. ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
121	ATCC # 98923	SignalTag 44-66
122	ATCC # 98920	SignalTag 67-90
123	ATCC # 98920	SignalTag 67-90
124	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
125	ECACC # 98121506	SignalTag 11121998
126	ECACC # 98121506	SignalTag 11121998
127	ECACC # 98121506	SignalTag 11121998
128	ECACC # 98121506	SignalTag 11121998
129	ECACC # 98121506	SignalTag 11121998
130	ECACC # 98121506	SignalTag 11121998
131	ECACC # 98121506	SignalTag 11121998
132	ECACC # 98121506	SignalTag 11121998
133	ECACC # 98121506	SignalTag 11121998
134	ECACC # 98121506	SignalTag 11121998
135	ECACC # 98121506	SignalTag 11121998
136	ECACC # 98121506	SignalTag 11121998
137	ECACC # 98121506	SignalTag 11121998
138	ECACC # 98121506	SignalTag 11121998
139	ECACC # 98121506	SignalTag 11121998
140	ECACC # 98121506	SignalTag 11121998

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	I ABLE VII	
Internal designation number	SEQ ID NO	Type of sequence
20-5-2-C3-CL0_4	40	DNA
20-8-4-A11-CL2_6	41	DNA
21-1-4-F2-CL11_1	42	DNA
22-11-2-H9-CL1_1	43	DNA
25-7-3-D4-CL0_2	44	DNA
26-27-3-D7-CLO_1	45	DNA
26-35-4-H9-CL1_1	46	DNA
26-45-2-C4-CL2_6	47	DNA
27-1-2-B3-CL0_1	48	DNA
27-1-2-B3-CL0_2	49	DNA
27-19-3-G7-CL11_2	50	DNA
33-10-4-E2-CL13_4	51	DNA
33-10-4-H2-CL2_2	52	DNA
33-110-4-A5-CL1_1	53	DNA
33-13-1-C1-CL1_1	54	DNA
33-30-2-A6-CL0_1	55	DNA
33-35-4-F4-CL1_2	56	DNA
33-35-4-G1-CL1_2	57	DNA
33-36-3-E2-CL1_1	58	DNA
33-36-3-E2-CL1_2	59	DNA
33-36-3-F2-CL2_2	60	DNA
33-4-2-G5-CL2_1	61	DNA
33-49-1-H4-CL1_1	62	DNA
33-66-2-B10-CL4_1	63	DNA
33-97-4-G8-CL2_2	64	DNA
33-98-4-C1-CL1_3	·65	DNA
47-14-1-C3-CL0_5	66	DNA
47-15-1-E11-CLO_1	67	DNA
47-15-1-H8-CLO_2	68	DNA
48-1-1-H7-CLO_1	69	DNA
48-1-1-H7-CLO_4	70	DNA
48-1-1-H7-CLO_5	71	DNA
48-3-1-H9-CLO_6	72	DNA
48-54-1-G9-CL2_1	73	DNA
		

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48-54-1-G9-CL3_1	74	DNA	
48-7-4-H2-CL2_2	75	DNA	
51-11-3-D5-CL1_3	76	DNA	
51-11-3-G9-CLO_1	77	DNA	
51-15-4-A12-CL11_3	78	DNA	
51-17-4-A4-CL3_1	79	DNA	
51-2-3-F10-CL1_5	80	DNA	
51-2-4-F5-CL11_2	81	DNA	
51-27-4-F2-CL0_2	82	DNA	
51-34-3-F8-CL0_2	83	DNA	
57-1-4-E2-CL1_2	84	DNA	
57-19-2-G8-CL2_1	85	DNA	
57-27-3-G10-CL2_2	86	DNA	
58-33-3-B4-CL1_2	87	DNA	
58-34-3-C9-CL1_2	88	DNA	
58-4-4-G2-CL2_1	89	DNA	
58-48-1-G3-CL2_4	90	DNA	
58-6-1-H4-CL1_1	91	DNA	
60-12-1-E11-CL1_2	92	DNA	
65-4-4-H3-CL1_1	93	DNA	
74-5-1-E4-CL1_2	94	DNA	
76-13-3-A9-CL1_2	95	DNA	
76-16-1-D6-CL1_1	96	DNA	
76-28-3-A12-CL1_5	97	DNA	
76-42-2-F3-CLO_1	98	DNA	
77-16-4-G3-CL1_3	99	DNA	
77-39-4-H4-CL11_4	100	DNA	
78-24-3-H4-CL2_1	101	DNA	
78-27-3-D1-CL1_6	102	DNA	
78-28-3-D2-CLO_2	103	DNA	
78-7-1-G5-CL2_6	104	DNA	
84-3-1-G10-CL11_6	105	DNA	
58-48-4-E2-CLO_1	106	DNA	
23-12-2-G6-CL1_2	107	DNA	
25-8-4-B12-CLO_5	108	DNA	
26-44-3-C5-CL2_1	109	DNA	
27-1-2-B3-CLO_3	110	DNA	

30-12-3-G5-CL0_1	111	DNA
33-106-2-F10-CL1_3	112	DNA
33-28-4-D1-CLO_1	113	DNA
33-31-3-C8-CL2_1	114	DNA
48-24-1-D2-CL3_2	115	DNA
48-46-4-A11-CL1_4	116	DNA
51-1-4-C1-CL0_2	117	DNA
51-39-3-H2-CL1_2	118	DNA
51-42-3-F9-CL1_1	119	DNA
51-5-3-G2-CLO_4	120	DNA
57-18-4-H5-CL2_1	121	DNA
76-23-3-G8-CL1_1	122	DNA
76-23-3-G8-CL1_3	123	DNA
78-8-3-E6-CL0_1	124	DNA
19-10-1-C2-CL1_3	125	DNA
33-11-1-B11-CL1_2	126	DNA
33-113-2-B8-CL1_2	127	DNA
33-19-1-C11-CL1_1	128	DNA
33-61-2-F6-CLO_2	129	DNA
47-4-4-C6-CL2_2	130	DNA
48-54-1-G9-CL1_1	131	DNA
51-43-3-G3-CL0_1	132	DNA
55-1-3-D11-CL0_1	133	DNA
58-14-2-D3-CL1_2	134	DNA
58-35-2-B6-CL2_3	135	DNA
76-18-1-F6-CL1_1	136	DNA
76-23-3-G8-CL2_2	137	DNA
76-30-3-B7-CL1_1	138	DNA
78-21-3-G7-CL2_1	139	DNA
58-45-4-B11-CL13_2	140	DNA
20-5-2-C3-CL0_4	141	PRT
20-8-4-A11-CL2_6	142	PRT
21-1-4-F2-CL11_1	143	PRT
22-11-2-H9-CL1_1	144	PRT
25-7-3-D4-CL0_2	145	PRT
26-27-3-D7-CLO_1	146	PRT
26-35-4-H9-CL1_1	147	PRT

26-45-2-C4-CL2_6	148	PRT
27-1-2-B3-CLO_1	149	PRT
27-1-2-B3-CL0_2	150	PRT
27-19-3-G7-CL11_2	151	PRT
33-10-4-E2-CL13_4	152	PRT
33-10-4-H2-CL2_2	153	PRT
33-110-4-A5-CL1_1	154	PRT
33-13-1-C1-CL1_1	155	PRT
33-30-2-A6-CLO_1	156	PRT
33-35-4-F4-CL1_2	157	PRT
33-35-4-G1-CL1_2	158	PRT
33-36-3-E2-CL1_1	159	PRT
33-36-3-E2-CL1_2	160	PRT
33-36-3-F2-CL2_2	161	PRT
33-4-2-G5-CL2_1	162	PRT
33-49-1-H4-CL1_1	163	PRT
33-66-2-B10-CL4_1	164	PRT
33-97-4-G8-CL2_2	165	PRT
33-98-4-C1-CL1_3	166	PRT
47-14-1-C3-CL0_5	167	PRT
47-15-1-E11-CLO_1	168	PRT
47-15-1-H8-CL0_2	169	PRT
48-1-1-H7-CLO_1	170	PRT
48-1-1-H7-CL0_4	171	PRT
48-1-1-H7-CL0_5	172	' PRT
48-3-1-H9-CLO_6	173	PRT
48-54-1-G9-CL2_1	174	PRT
48-54-1-G9-CL3_1	175	PRT
48-7-4-H2-CL2_2	176	PRT
51-11-3-D5-CL1_3	177	PRT
51-11-3-G9-CLO_1	178	PRT
51-15-4-A12-CL11_3	179	PRT
51-17-4-A4-CL3_1	180	PRT
51-2-3-F10-CL1_5	181	PRT
51-2-4-F5-CL11_2	182	PRT
51-27-4-F2-CL0_2	183	PRT
51-34-3-F8-CLO_2	184	PRT

57-1-4-E2-CL1_2	185	PRT
57-19-2-G8-CL2_1	186	PRT
57-27-3-G10-CL2_2	. 187	PRT
58-33-3-B4-CL1_2	188	PRT
58-34-3-C9-CL1_2	189	PRT
58-4-4-G2-CL2_1	190	PRT
58-48-1-G3-CL2_4	191	PRT
58-6-1-H4-CL1_1	192	PRT
60-12-1-E11-CL1_2	193	PRT
65-4-4-H3-CL1_1	194	PRT
74-5-1-E4-CL1_2	195	PRT
76-13-3-A9-CL1_2	196	PRT
76-16-1-D6-CL1_1	197	PRT
76-28-3-A12-CL1_5	198	PRT
76-42-2-F3-CLO_1	199	PRT
77-16-4-G3-CL1_3	200	PRT
77-39-4-H4-CL11_4	201	PRT
78-24-3-H4-CL2_1	202	PRT
78-27-3-D1-CL1_6	203	PRT
78-28-3-D2-CLO_2	204	PRT
78-7-1-G5-CL2_6	205	PRT
84-3-1-G10-CL11_6	206	PRT
58-48-4-E2-CLO_1	207	PRT
23-12-2-G6-CL1_2	208	PRT
25-8-4-B12-CL0_5	209	PRT
26-44-3-C5-CL2_1	210	PRT
27-1-2-B3-CL0_3	211	PRT
30-12-3-G5-CL0_1	212	PRT
33-106-2-F10-CL1_3	213	PRT
33-28-4-D1-CLO_1	214	PRT
33-31-3-C8-CL2_1	215	PRT
48-24-1-D2-CL3_2	216	PRT
48-46-4-A11-CL1_4	217	PRT
51-1-4-C1-CL0_2	218	PRT
51-39-3-H2-CL1_2	219	PRT
51-42-3-F9-CL1_1	220	PRT
51-5-3-G2-CL0_4	221	PRT

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57-18-4-H5-CL2_1	222	PRT
76-23-3-G8-CL1_1	223	PRT
76-23-3-G8-CL1_3	224	PRT
78-8-3-E6-CLO_1	225	PRT
19-10-1-C2-CL1_3	226	PRT
33-11-1-B11-CL1_2	227	PRT
33-113-2-B8-CL1_2	228	PRT
33-19-1-C11-CL1_1	229	PRT
33-61-2-F6-CLO_2	230	PRT
47-4-4-C6-CL2_2	231	PRT
48-54-1-G9-CL1_1	232	PRT
51-43-3-G3-CLO_1	233	PRT
55-1-3-D11-CLO_1	234	PRT
58-14-2-D3-CL1_2	235	PRT
58-35-2-B6-CL2_3	236	PRT
76-18-1-F6-CL1_1	237	PRT
76-23-3-G8-CL2_2	238	PRT
76-30-3-B7-CL1_1	239	PRT
78-21-3-G7-CL2_1	240	PRT
58-45-4-B11-CL13_2	241	PRT
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20-8-4-A11-FL2	243	DNA
22-6-2-C1-FL2	244	DNA
22-11-2-H9-FL1	245	DNA
23-8-3-B1-FL1	246	DNA
24-3-3-C6-FL1	247	DNA
24-4-1-H3-FL1	248	DNA
26-45-2-C4-FL2	249	DNA
26-48-1-H10-FL1	250	DNA
26-49-1-A5-FL2	251	DNA
30-6-4-E3-FL3	252	DNA
33-6-1-G11-FL1	253	DNA
33-8-1-A3-FL2	254	DNA
33-11-3-C6-FL1	255	DNA
33-14-4-E1-FL1	256	DNA
33-21-2-D5-FL1	257	DNA
33-26-4-E10-FL1	258	DNA

33-27-1-E11-FL1	259	DNA
33-28-4-D1-FL1	260	DNA
33-28-4-E2-FL2	261	DNA
33-30-4-C4-FL1	262	DNA
33-35-4-F4-FL1	263	DNA
33-36-3-F2-FL2	264	DNA
33-52-4-F9-FL2	265	DNA
33-52-4-H3-FL1	266	DNA
33-59-1-B7-FL1	267	DNA
33-71-1-A8-FL1	268	DNA
33-72-2-B2-FL1	269	DNA
33-105-2-C3-FL1	270	DNA
33-107-4-C3-FL1	271	DNA
33-110-2-G4-FL1	272	DNA
47-7-4-D2-FL2	273	DNA
47-10-2-G12-FL1	274	DNA
47-14-3-D8-FL1	275	DNA
47-18-3-C2-FL1	276	DNA
47-18-3-G5-FL2	277	DNA
47-18-4-E3-FL2	278	DNA
48-3-1-H9-FL3	279	DNA
48-4-2-H3-FL1	280	DNA
48-6-1-C9-FL1	281	DNA
48-7-4-H2-FL2	282	DNA
48-8-1-D8-FL3	283	DNA
48-13-3-H8-FL1	284	DNA
48-19-3-A7-FL1	285	DNA
48-19-3-G1-FL1	286	DNA
48-25-4-D8-FL1	287	DNA
48-21-4-H4-FL1	288	DNA
48-26-3-88-FL2	289	DNA
48-29-1-E2-FL1	290	DNA
48-31-3-F7-FL1	291	DNA
48-47-3-A5-FL1	292	DNA
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51-1-4-E9-FL3	294	DNA
51-1-4-E9-FL2	295	DNA

51-2-1-E10-FL1	296	DNA
51-2-3-F10-FL1	297	DNA
51-2-4-F5-FL1	298	DNA
51-3-3-B10-FL2	299	DNA
51-3-3-B10-FL3	300	DNA
51-7-3-G3-FL1	301	DNA
51-10-3-D11-FL1	302	DNA
51-11-3-D5-FL1	303	DNA
51-13-1-F7-FL3	304	DNA
51-15-4-H10-FL1	305	DNA
51-17-4-A4-FL1	306	DNA
51-18-1-C3-FL1	307	DNA
51-25-3-F3-FL1	308	DNA
51-27-1-E8-FL1	309	DNA
51-28-2-G1-FL2	310	DNA
51-39-3-H2-FL1	311	DNA
51-42-3-F9-FL1	312	DNA
51-44-4-H4-FL1	313	DNA
55-1-3-H10-FL1	314	DNA
55-5-4-A6-FL1	315	DNA
58-26-3-D1-FL1	316	DNA
57-18-1-D5-FL1	317	DNA
57-27-3-A11-FL1	318	DNA
57-27-3-G10-FL2	319	DNA
58-10-3-D12-FL1	320	DNA
58-11-1-G10-FL1	321	DNA
58-11-2-G8-FL2	322	DNA
58-36-3-A9-FL2	323	DNA
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58-53-2-B12-FL2	328	DNA
59-9-4-A10-FL1	329	DNA
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60-17-3-G8-FL2	331	DNA
62-5-4-B10-FL1	332	DNA

65-4-4-H3-FL1	333	DNA
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76-4-1-G5-FL1	335	DNA
76-7-3-A12-FL1	336	DNA
76-16-4-C9-FL3	337	DNA
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77-5-4-E7-FL1	340	DNA
77-11-1-A3-FL1	341	DNA
77-16-3-D7-FL1	342	DNA
77-16-4-G3-FL1	343	DNA
77-25-1-A6-FL1	344	DNA
77-26-2-F2-FL3	345	DNA
78-6-2-E3-FL2	346	DNA
78-7-1-G5-FL2	347	DNA
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78-18-3-B4-FL3	349	DNA
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78-24-2-B8-FL1	352	DNA
78-24-3-A8-FL1	353	DNA
78-24-3-H4-FL2	354	DNA
78-25-1-F11-FL1	355	DNA
78-26-1-B5-FL1	356	DNA
78-27-3-D1-FL1	357	DNA
78-29-1-B2-FL1	358	DNA
78-29-4-B6-FL1	359	DNA
14-1-3-E6-FL1	360	DNA
30-9-1-G8-FL2	361	DNA
33-10-4-H2-FL2	362	DNA
33-10-4-H2-FL1	363	DNA
74-10-3-C9-FL2	364	DNA
33-97-4-G8-FL3	365	DNA
33-97-4-G8-FL2	366	DNA
33-104-4-H4-FL1	367	DNA
47-2-3-B3-FL1	368	DNA
47-37-4-G11-FL1	369	DNA

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57-25-1-F10-FL2	370	DNA
58-19-3-D3-FL1	371	DNA
58-34-3-C9-FL2	372	DNA
58-48-4-E2-FL2	373	DNA
76-21-1-C4-FL1	374	DNA
78-26-2-H7-FL1	375	DNA
77-20-2-E11-FL1	376	DNA
47-1-3-F7-FL2	377	DNA
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20-8-4-A11-FL2	379	PRT
22-6-2-C1-FL2	380	PRT
22-11-2-H9-FL1	381	PRT
23-8-3-B1-FL1	382	PRT
24-3-3-C6-FL1	383	PRT
24-4-1-H3-FL1	384	PRT
26-45-2-C4-FL2	385	PRT
26-48-1-H10-FL1	386	PRT
26-49-1-A5-FL2	387	PRT
30-6-4-E3-FL3	388	PRT
33-6-1-G11-FL1	389	PRT
33-8-1-A3-FL2	390	PRT
33-11-3-C6-FL1	391	PRT
33-14-4-E1-FL1	392	PRT
33-21-2-D5-FL1	393	PRT
33-26-4-E10-FL1	394	PRT
33-27-1-E11-FL1	395	PRT
33-28-4-D1-FL1	396	PRT
33-28-4-E2-FL2	397	PRT
33-30-4-C4-FL1	398	PRT
33-35-4-F4-FL1	399	PRT
33-36-3-F2-FL2	400	PRT
33-52-4-F9-FL2	401	PRT
33-52-4-H3-FL1	402	PRT
33-59-1-B7-FL1	403	PRT
33-71-1-A8-FL1	404	PRT
33-72-2-B2-FL1	405	PRT
33-105-2-C3-FL1	406	PRT

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33-107-4-C3-FL1	407	PRT
33-110-2-G4-FL1	408	PRT
47-7-4-D2-FL2	409	PRT
47-10-2-G12-FL1	410	PRT
47-14-3-D8-FL1	411	PRT
47-18-3-C2-FL1	412	PRT
47-18-3-G5-FL2	413	PRT
47-18-4-E3-FL2	414	PRT
48-3-1-H9-FL3	415	PRT
. 48-4-2-H3-FL1	416	PRT
48-6-1-C9-FL1	417	PRT
48-7-4-H2-FL2	418	PRT
48-8-1-D8-FL3	419	PRT
48-13-3-H8-FL1	420	PRT
48-19-3-A7-FL1	421	PRT
48-19-3-G1-FL1	422	PRT
48-25-4-D8-FL1	423	PRT
48-21-4-H4-FL1	424	PRT
48-26-3-B8-FL2	425	PRT
48-29-1-E2-FL1	426	PRT
48-31-3-F7-FL1	427	PRT
48-47-3-A5-FL1	428	PRT
51-1-1-G12-FL1	429	PRT
51-1-4-E9-FL3	430	PRT
51-1-4-E9-FL2	431	PRT
51-2-1-E10-FL1	432	PRT
51-2-3-F10-FL1	433	PRT
51-2-4-F5-FL1	434	PRT
51-3-3-B10-FL2	435	PRT
51-3-3-B10-FL3	436	PRT
51-7-3-G3-FL1	437	PRT
51-10-3-D11-FL1	438	PRT
51-11-3-D5-FL1	439	PRT
51-13-1-F7-FL3	440	PRT
51-15-4-H10-FL1	441	PRT
51-17-4-A4-FL1	442	PRT
51-18-1-C3-FL1	443	PRT

51-25-3-F3-FL1	444	PRT
51-27-1-E8-FL1	445	PRT
51-28-2-G1-FL2	446	PRT
51-39-3-H2-FL1	447	PRT
51-42-3-F9-FL1	448	PRT
51-44-4-H4-FL1	449	PRT
55-1-3-H10-FL1	450	PRT
55-5-4-A6-FL1	451	PRT
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57-18-1-D5-FL1	453	PRT
57-27-3-A11-FL1	454	PRT
57-27-3-G10-FL2	455	PRT
58-10-3-D12-FL1	456	PRT
58-11-1-G10-FL1	457	PRT
58-11-2-G8-FL2	458	PRT
58-36-3-A9-FL2	459	PRT
58-38-1-A2-FL2	460	PRT
58-38-1-E5-FL1	461	PRT
58-44-2-B3-FL3	462	PRT
58-45-3-H11-FL1	463	PRT
58-53-2-B12-FL2	464	PRT
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60-16-3-A6-FL1	466	PRT
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76-7-3-A12-FL1	472	PRT
76-16-4-C9-FL3	473	PRT
76-30-3-B7-FL1	474	PRT
77-5-1-C2-FL1	475	PRT
77-5-4-E7-FL1	476	PRT
77-11-1-A3-FL1	477	PRT
77-16-3-D7-FL1	478	PRT
77-16-4-G3-FL1	479	PRT
77-25-1-A6-FL1	480	PRT

77-26-2-F2-FL3	481	PRT
78-6-2-E3-FL2	482	PRT
78-7-1-G5-FL2	483	PRT
78-16-2-C2-FL1	484	PRT
78-18-3-B4-FL3	485	PRT
78-20-1-G11-FL1	486	PRT
78-22-3-E10-FL1	487	PRT.
78-24-2-B8-FL1	488	PRT
78-24-3-A8-FL1	489	PRT
78-24-3-H4-FL2	490	PRT
78-25-1-F11-FL1	491	PRT
78-26-1-B5-FL1	492	PRT
78-27-3-D1-FL1	493	PRT
78-29-1-B2-FL1	494	PRT
78-29-4-B6-FL1	495	PRT
14-1-3-E6-FL1	496	PRT
30-9-1-G8-FL2	497	PRT
33-10-4-H2-FL2	498	PRT
33-10-4-H2-FL1	499	PRT
74-10-3-C9-FL2	500	PRT
33-97-4-G8-FL3	501	PRT
33-97-4-G8-FL2	502	PRT
33-104-4-H4-FL1	503	PRT
47-2-3-B3-FL1	504	PRT
47-37-4-G11-FL1	505	PRT
57-25-1-F10-FL2	506	PRT
58-19-3-D3-FL1	507	PRT
58-34-3-C9-FL2	508	PRT
58-48-4-E2-FL2	509	PRT
76-21-1-C4-FL1	510	PRT
78-26-2-H7-FL1	511	PRT
77-20-2-E11-FL1	512	PRT
47-1-3-F7-FL2	513	PRT

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TABLE VIII

ID	Locations	PROSITE Signature Name
195	110-121	Aldehyde dehydrogenases csyteine active site
221	28-37	ATP synthase alpha and beta subunits signature
223	171-181	Regulator of chromosome condensation (RCC1) signature 2
225	90-112	Phosphatidylethanolamine-binding protein family signature
226	10.34	Protein kinases ATP-binding region signature

WHAT IS CLAIMED IS:

- A purified or isolated nucleic acid comprising the sequence of one of SEQ ID NOs: 40-140 and 242 377 or a sequence complementary thereto.
- 2. A purified or isolated nucleic acid comprising at least 10 consecutive bases of the sequence of one of 5 SEQ ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto.
 - 3. A purified or isolated nucleic acid comprising the full coding sequences of one of SEQ ID NOs: 40, 42-44, 46, 48, 49, 51, 53, 60, 62-72, 76-78, 80-83, 85-88, 90, 93, 94, 97, 99-102, 104, 107-125, 127, 132, 135-138, 140 and 242-377wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein.
- 4. A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein.
- 5. A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140 and 242-377 which encode the signal peptide.
 - 6. A purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEQ ID NOs: 141-241 and 378-513.
- A purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-20
 189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.
 - 8. A purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEO ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.
 - A purified or isolated protein comprising the sequence of one of SEO ID NOs: 141-241 and 378-513.
- 25 10. A purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513.
 - 11. An isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.
- 30 12. An isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.
 - 13. A method of making a protein comprising one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of:

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obtaining a cDNA comprising one of the sequences of sequence of SEQ ID NO: 40-140 and 242-377; inserting said cDNA in an expression vector such that said cDNA is operably linked to a promoter; and introducing said expression vector into a host cell whereby said host cell produces the protein encoded by said cDNA.

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- 5 14. The method of Claim 13, further comprising the step of isolating said protein.
 - 15. A protein obtainable by the method of Claim 14.
 - 16. A host cell containing a recombinant nucleic acid of Claim 1.
 - 17. A purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEQ ID NOs: 141-241 and 378-513.
- 10 18. In an array of polynucleotides of at least 15 nucleotides in length, the improvement comprising inclusion in said array of at least one of the sequences of SEQ ID NOs: 40-140 and 242-377, or one of the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or a fragment thereof of at least 15 consecutive nucleotides.
- A purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent
 conditions to the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary to one of the sequences of SEQ ID NOs: 40-140 and 242-377.
 - 20. A purified or isolated antibody capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of SEQ ID NOs: 141-241 and 378-513.

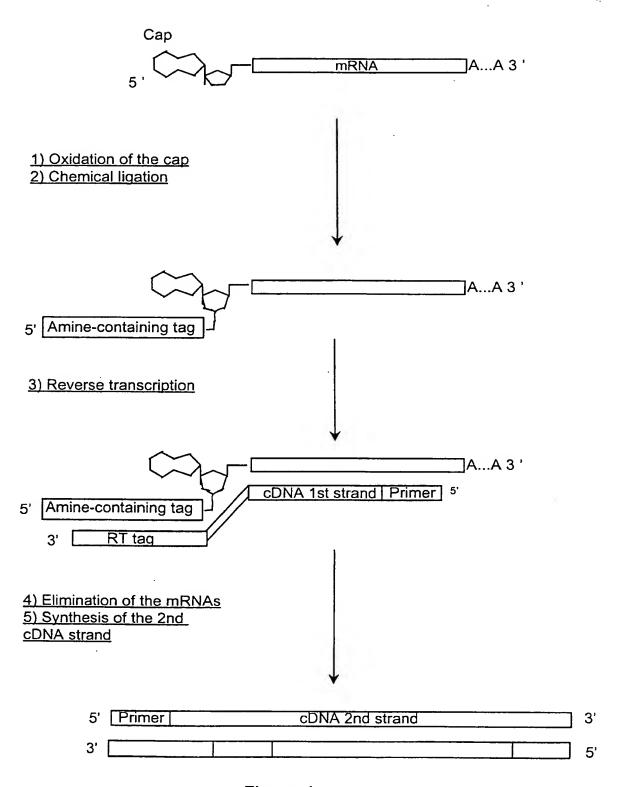
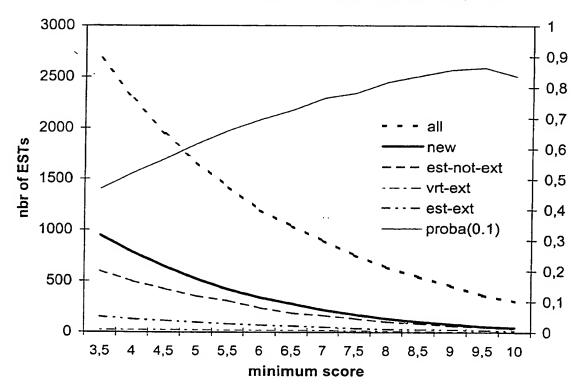


Figure 1

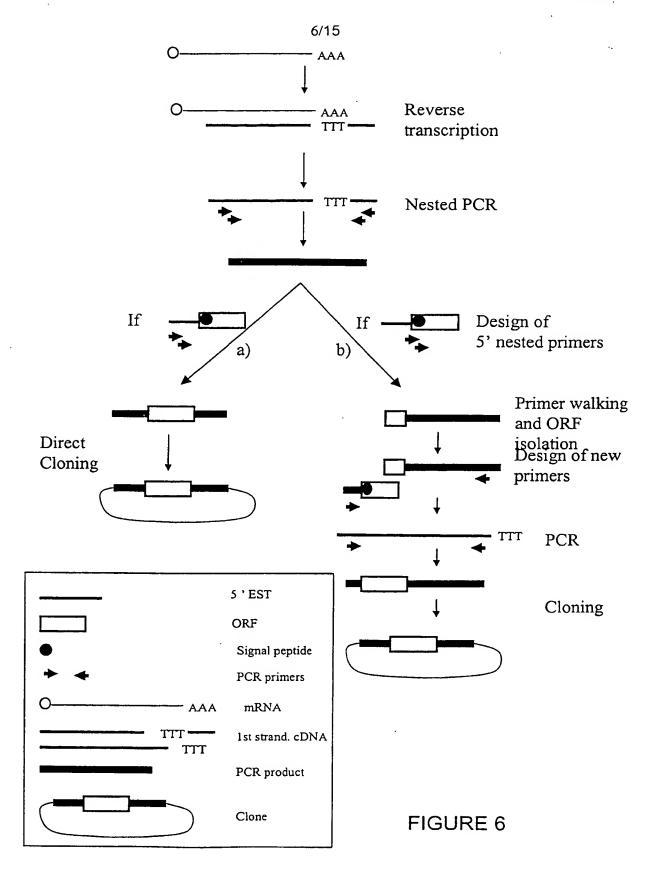
Minimum signal peptide score	false positive rate	false negative rate	proba(0.1)	proba(0.2)
3,5	0,121	0,036	0,467	0,664
4	0,096	0,06	0,519	0,708
4,5	0,078	0,079	0,565	0,745
5	0,062	0,098	0,615	0,782
5,5	0,05	0,127	0,659	0,813
6	0,04	0,163	0,694	0,836
6,5	0,033	0,202	0,725	0,855
7	0,025	0,248	0,763	0,878
7,5	0,021	0,304	0,78	0,889
8	0,015	0,368	0,816	0,909
8,5	0,012	0,418	0,836	0,92
9	0,009	0,512	0,856	0,93
9,5	0,007	0,581	0,863	0,934
10	0,006	0,679	0,835	0,919

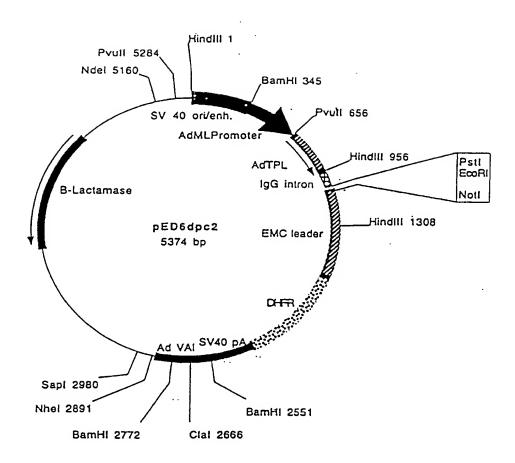
influence of minimum score on signal peptide recognition



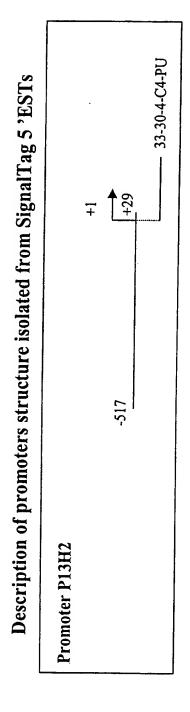
Minimum signal peptide score		New ESTs	ESTs matching public EST closer than 40 bp from beginning	ESTs extending known mRNA more than 40 bp	ESTs extending public EST more than 40 bp
3,5	2674	947	599	23	150
4	2278	784	499	23	126
4,5	1943	647	425	22	112
5	1657	523	353	21	96
5,5	1417	419	307	19	80
6	1190	340	238	18	68
6,5	1035	280	186	18	60
7	893	219	161	15	48
7,5	753	173	132	12	36
8	636	133	101	11	29
8,5	543	104	83	8	26
9	456	81	. 63	6	24
9,5	364	57	48	6	18
10	303	47	35	6	15

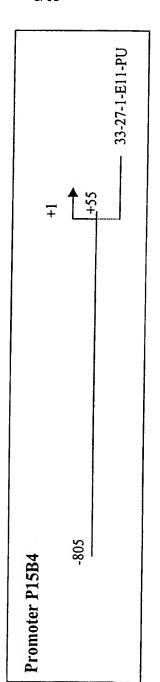
				•	
Tissue	· All ESTs	New ESTs	ESTs matching public EST closer than 40 bp from beginning	ESTs extending known mRNA more than 40 bp	ESTs extending public EST more than 40 bp
Brain	329	131	75	3	24
Cancerous prostate	134	40	37	1	6
Cerebellum	17	9	1	0	6
Colon	21	11	4	0	o
Dystrophic muscle	41	18	8	Ō	1
Fetal brain	70	37	16	Ō	1
Fetal kidney	227	116	46	1	19
Fetal liver	13	7	2	0	o
Heart	30	15	7	0	1
Hypertrophic prostate	86	23	22	2	2
Kidney	10	7	3	0	0
Large intestine	21	8	4	0	1
Liver	23	9	6	0	o
Lung	24	12	4	0	1
Lung (cells)	57	38	6	0	4
Lymph ganglia	163	60	23	2	12
Lymphocytes	23	6	4	0	2
Muscle	33	16	6	0	4
Normal prostate	181	61	45	7	11
Ovary	90	57	12	1	2
Pancreas	48	11	6	0	1
Placenta	24	5	1	0	0
Prostate	34	16	4	0	2
Spleen	56	28	10	0	1
Substantia nigra	108	47	27	1	6
Surrenals	15	3	3	1	0
Testis	131	68	25	1	8
Thyroid	17	8	2	0	2
Umbilical cord	55	17	12	1	8 2 3
Uterus	28	15	3	0	2
Non tissue-specific	568	48	177	2	28
Total	2677	947	601	23	150





Plasmid name: pED6dpc2 Plasmid size: 5374 bp 8/15





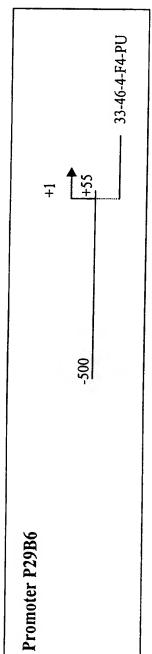


FIGURE 8

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Description of Transcription Factor Binding Sites present on promoters isolated from SignalTag sequences

Promoter sequence P13H2 (546 bp):

Matrix	Position	Orientation	Score	Length	Sequence
CMYB_01	-502	+	0.983	9	TGTCAGTTG
MYOD_Q6	-501	- .	0.961	10	CCCAACTGAC
S8_01	-444	•	0.960	11	AATAGAATTAG
S8_01	-425	+	0.966	11	AACTAAATTAG
DELTAEF1_01	-390	•	0.960	11	GCACACCTCAG
GATA_C	-364	-	0.964	11	AGATAAATCCA
CMYB_01	-349	+	0.958	9	CTTCAGTTG
GATA1_02	-343	+	0.959	14	TTGTAGATAGGACA
GATA_C	-339	+	0.953	11	AGATAGGACAT
TAL1ALPHAE47_01	-235	+	0.973	16	CATAACAGATGGTAAG
TAL1BETAE47_01	-235	+	0.983	16	CATAACAGATGGTAAG
TAL1BETAITF2_01	-235	+	0.978	16	CATAACAGATGGTAAG
MYOD_Q6	-232	-	0.954	10	ACCATCTGTT
GATA1_04	-217	•	0.953	13	TCAAGATAAAGTA
IK1_01	-126	+	0.963	13	AGTTGGGAATTCC
IK2_01	-126	+	0.985	12	AGTTGGGAATTC
CREL_01	-123	+	0.962	10	TGGGAATTCC
GATA1_02	-96	+	0.950	14	TCAGTGATATGGCA
SRY_02	-41	-	0.951	12	TAAAACAAAACA
E2F_02	-33	+	0.957	8	TTTAGCGC
MZF1_01	-5	-	0.975	8	TGAGGGGA

Promoter sequence P15B4 (861bp):

Matrix	Position	Orientation	Score	Length	Sequence
NFY_Q6	-748	-	0.956	11	GGACCAATCAT
MZF1_01	-738	+	0.962	8	CCTGGGGA
CMYB_01	-684	, +	0.994	9	TGACCGTTG
VMYB_02	-682		0.985	9	TCCAACGGT
STAT_01	-673	+	0.968	9	TTCCTGGAA
STAT_01	-673	-	0.951	9	TTCCAGGAA
MZF1_01	-556	-	0.956	8	TTGGGGGA
IK2_01	-451	+	0.965	12	GAATGGGATTTC
MZF1_01	-424	+	0.986	8	AGAGGGGA
SRY_02	-398	-	0.955	12	GAAAACAAAACA
MZF1_01	-216	+	0.960	8	GAAGGGGA
MYOD_Q6	-190	+	0.981	10	AGCATCTGCC
DELTAEF1_01	-176	+	0.958	11	TCCCACCTTCC
S8_01	5	-	0.992	11	GAGGCAATTAT
MZF1_01	16	-	0.986	8	AGAGGGGA

Promoter sequence P29B6 (555 bp):

Matrix	Position	Orientation	Score	Length	Sequence
ARNT_01	-311	+	0.964	16	GGACTCACGTGCTGCT
NMYC_01	-309	+	0.965	12	ACTCACGTGCTG
USF_01	-309	+	0.985	12	ACTCACGTGCTG
USF_01	-309	-	0.985	12	CAGCACGTGAGT
NMYC_01	-309	•	0.956	12	CAGCACGTGAGT
MYCMAX_02	-309	-	0.972	12	CAGCACGTGAGT
USF_C	-307	+	0.997	8	TCACGTGC
USF_C	-307	•	0.991	8	GCACGTGA
MZF1_01	-292	•	0.968	8	CATGGGGA
ELK1_02	-105	+	0.963	14	CTCTCCGGAAGCCT
CETS1P54_01	-102	+	0.974	10	TCCGGAAGCC
AP1_Q4	-42	•	0.963	11	AGTGACTGAAC
AP1FJ_Q2	-42	•	0.961	11	AGTGACTGAAC
PADS_C	45	+	1.000	9	TGTGGTCTC

Figure 9

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100.0% identity in 125 aa overlap

SEQ ID NO: 217 MADEELEALRRORLAELOAKHGDPGDAAOOEAKHREAEMRNSILAOVLDOSARARLSNLA SEQ ID NO: 516 MADEELEALRRQRLAELQAKHGDPGDAAQQEAKHREAEMRNSILAQVLDQSARARLSNLA SEQ ID NO: 217 LVKPEKTKAVENYLIQMARYGQLSEKVSEQGLIEILKKVSQQTEKTTTVKFNRRKVMDSD SEQ ID NO: 516 LVKPEKTKAVENYLIQMARYGQLSEKVSEQGLIEILKKVSQQTEKTTTVKFNRRKVMDSD

SEQ ID NO: 217 EDDDY ::::X
SEQ ID NO: 516 EDDDY

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CLUSTAL W(1.5) multiple sequence alignment

SEQ	ID	NO:	517 [°]	MFCPLKLILLPVLLDYSLGLNDLNVSPPELTVHVGDSALMGCVFQSTEDKCIFKIDWTLS
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SEQ	ID	NO:	174	MGCVFOSTEDKRIFKIDWTLS
SEQ	ID	NO:	175	MGCVFQSTVDKCIFKIDWTLS
-				******
SEQ	ID	NO:	517	PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDNLCNDGSLLLQDVQDVE
SEO	ID	NO:	232	PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRL
_			174	PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDNLCNDGSLLLQDVQEADQGTYICEIRL
-			175	PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRL
ODQ	110	1.0.	1,3	**************************************
SEO	TD	MO:	517	
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_			174	
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SEQ	מנ	NO:	1/5	KGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAK
CEO	T.D.	170	F 1 5	
_		NO:		
		NO:		
_		NO:		IVFRYYHKLRMSAEYSQSWGHFQNRVNLVGDIFRNDGSIMLQGVRESDGGNYTCSIHLGN
SEQ	ID	NO:	175	VTRRKHHCVREGSG
SEQ	ID	NO:	517	
SEQ	ID	NO:	232	
SEQ	ID	NO:	174	LVFKKTIVLHVSPEEPRTLVTPAALRPLVLGGNQLVIIVGIVCATILLLPVLILIVKKTC
SEQ	ID :	NO:	175	
SEQ	ID :	NO:	517	
SEQ				••••••
SEO				GNKSSVNSTVLVKNTKKTNP
SEQ				GNASSVNSIVLVANIAAINP
SEQ	י עב	MO:	T/2	

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99.6% identity in 225 aa overlap SEQ ID NO: 515 PTAVQKEEARQDVEALLSRTVRTQILTGKELRVATQEKEGSSGRCMLTLLGLSFILAGLI ************************ SEQ ID NO: 231 LRVATQEKEGSSGRCMLTLLGLSFILAGLI SEQ ID NO: 515 VGGACIYKYFMPKSTIYRGEMCFFDSEDPANSLRGGEPNFLPVTEEADIREDDNIAIIDV SEQ ID NO: 231 VGGACIYKYFMPKSTIYRGEMCFFDSEDPANSLRGGEPNFLPVTEEADIREDDNIAIIDV SEQ ID NO: 515 PVPSFSDSDPAAIIHDFEKGMTAYLDLLLGNCYLMPLNTSIVMPPKNLVELFGKLASGRY SEQ ID NO: 231 PVPSFSDSDPAAIIHDFEKGMTAYLDLLLGICYLMPLNTSIVMPPKNLVELFGKLASGRY SEQ ID NO: 515 LPQTYVVREDLVAVEEIRDVSNLGIFIYQLCNNRKSFRLRRRDLLLGFNKRAIDKCWKIR SEQ ID NO: 231 LPQTYVVREDLVAVEEIRDVSNLGIFIYQLCNNRKSFRLRRRDLLLGFNKRAIDKCWKIR

SEQ ID NO: 515 HFPNEFIVETKICQE SEQ ID NO: 231 HFPNEFIVETKICQE

13/15

99.7% identity in 353 aa overlap SEO ID NO:196 MERGLKSADPRDGTGYTGWAGIAVLYLHLY SEQ ID NO:518 LAEGYFDAAGRLTPEFSQRLTNKIRELLQQMERGLKSADPRDGTGYTGWAGIAVLYLHLY SEQ ID NO:196 DVFGDPAYLQLAHGYVKQSLNCLTKRSITFLCGDAGPLAVAAVLYHKMNNEKOAEDCITR SEQ ID NO:518 DVFGDPAYLQLAHGYVKQSLNCLTKRSITFLCGDAGPLAVAAVLYHKMNNEKQAEDCITR SEQ ID NO:196 LIHLNKIDPHAPNEMLYGRIGYIYALLFVNKNFGVEKTPOSHIOOICETILTSGENLARK SEQ ID NO:518 LIHLNKIDPHAPNEMLYGRIGYIYALLFVNKNFGVEKIPQSHIQQICETILTSGENLARK SEQ ID NO:196 RNFTAKSPLMYEWYQEYYVGAAHGLAGIYYYLMQPSLQVSQGKLHSLVKPSVDYVCQLKF SEQ ID NO:518 RNFTAKSPLMYEWYQEYYVGAAHGLAGIYYYLMQPSLQVSQGKLHSLVKPSVDYVCQLKF SEQ ID NO:196 PSGNYPPCIGDNRDLLVHWCHGAPGVIYMLIQAYKVFREEKYLCDAYQCADVIWQYGLLK SEQ ID NO:518 PSGNYPPCIGDNRDLLVHWCHGAPGVIYMLIQAYKVFREEKYLCDAYQCADVIWQYGLLK SEQ ID NO:196 KGYGLCHGSAGNAYAFLTLYNLTQDMKYLYRACKFAEWCLEYGEHGCRTPDTPFSLFEGM SEQ ID NO:518 KGYGLCHGSAGNAYAFLTLYNLTQDMKYLYRACKFAEWCLEYGEHGCRTPDTPFSLFEGM SEQ ID NO:196 AGTIYFLADLLVPTKARFPAFEL SEQ ID NO:518 AGTIYFLADLLVPTKARFPAFEL

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98.5% identity in 194 aa overlap SEQ ID NO:519 ARNLPPLTDAQKNKLRHLSVVTLAAKVKCIPYAVLLEALALRNVROLEDLVIEAVYADVL SEQ ID NO:158 ARNLPPLTEAQKNKLRHLSVVTLAAKVKCIPYAVLLEALALRNVRQLEDLVIEAVYADVL SEQ ID NO:519 RGSLDQRNQRLEVDYSIGRDIQRQDLSAIAQTLQEWCVGCEVVLSGIEEQVSRANQHKEQ SEQ ID NO:158 RGSLDQRNQRLEVDYSIGRDIQRQDLSAIARTLQEWCVGCEVVLSGIEEQVSRANQHKEQ SEQ ID NO:519 QLGLKQQIESEVANLKKTIKVTTAAAAAATSQDPEQHLTELREPASGTNQRQPSKKASKG SEQ ID NO:158 QLGLKQQIESEVANLKKTIKVTTAAAAAATSQDPEQHLTELREPAPGTNQRQPSKKASKG SEQ ID NO:519 KGLRGSAKIWSKSN SEQ ID NO:158 KGLRGSAKIWSKSN 88.7% identity in 62 aa overlap SEQ ID NO:519 MSAEVKVTGQNQEQFLLLAKSAKGAALATLIHQVLEAPGVYVFGELLDMPNVRELAESDF SEQ ID NO:158 MSAEVKVTGQNQEQFLLLAKSAKGAALATLIHQVLEAPGVYVFGELLDMPNVRELXARNL

SEQ ID NO:519 AS .X SEQ ID NO:158 PP

15/15

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FIGURE 15

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IIII A.	14 110	ייים	-5		7,20	• • •	01)	1				5			
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gaa c	ga gaa	ada	aga	age	Tie	agu	gac	Com	9ac	Clu	LCU	772	202	23-	
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40	ne rro	~- 9	1 110	45				9	50					55	
						~~~	a++	cat		~~~	224	+ > > :		-	354
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Pro G	lu Ser	Ala		Thr	Thr	Pro	ьeи		ser	GIU	ьуs				
			60					65							
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Met Trp Trp Phe	
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1 5 10 15	
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Lys Cys Leu Phe Gly Ala Met Leu Asn Ile Ala Ala Val Leu Cys Gln	
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Lys	660
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722

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Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala Ser Ala Gly
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Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln Cys Phe Lys
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gtc agc agc tgg acg gag tgc ccg ccc acc tgg tgc agc ccg ctg gac
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Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser Pro Leu Asp
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Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Lys Trp Ser Val
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Arg Val Leu Leu Ser Lys Arg Cys Ala Pro Arg Cys Pro Asn Asp Asn
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Met Xaa Phe Glu Trp Ser Pro Ala Pro Met Val Gln Gly Val Ile Thr
                             75
                                                 RΛ
        70
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Arg Arg Cys Cys Ser Trp Ala Leu Cys Asn Arg Ala Leu Thr Pro Gln
                                             95
                        90
                                                                       441
gag ggg cgc tgg gcc ctg cra ggg ggg ctc ctg ctc cag gac cct tcg
Glu Gly Arg Trp Ala Leu Xaa Gly Gly Leu Leu Gln Asp Pro Ser
                                         110
                     105
 agg ggc ara aaa acc tgg gtg cgg cca cag ctg ggg ctc cca ctc tgc
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Arg Gly Xaa Lys Thr Trp Val Arg Pro Gln Leu Gly Leu Pro Leu Cys
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                                                                       534
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Asp Gln Thr Leu Glu Phe Leu Lys Ile Pro Ser Thr Leu Ala Pro Pro

•																
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_				_	gca		_									532
Cys	Ile	11e 140	Ile	Val	Ala	Ile	A1a 145	Leu	Leu	Ile	Leu	Ser 150	GIY	He	Trp	
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Gln	Arg 155	Xaa	Xaa	Lys	Asn	Lys 160	Glu	Pro	Ser	Glu	Val 165	Asp	Asp	Ala	Glu	
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		_	-		Met				_						_	
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ccc	ctg	gac	atg	aag	gga	999	cat	att	aat	gat	gcc	ttc	atg	aca	gag	676
Pro	Leu	Asp	Met	Lys	Gly	Gly	His	Ile	Asn	Asp	Ala	Phe	Met	Thr	Glu	
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Asp	Glu	Arg	Leu 205	Thr	Pro	Leu				•						
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Dea .		-15	501		Deu		-10					-5				
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gca																192
Ala	vaı	гуs	ASII	Asp 20	Pne	GIII	116	тър	25	Leu	116	Cys	Gry	30	TIC	
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aat																288
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Phe 1														Leu		336
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pro s																432
Phe													taai	taaat	tt	481
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                -35
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Trp Lys Asp Lys Val Val Asp Leu Leu Tyr Trp Arg Asp Ile Lys Lys
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Gln Ile Asp His Tyr Leu Val Leu Ala Asn Lys Asn Val Lys Asp Ala
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Met Arg Gln Lys Arg Lys Gly Asp 1 5 ctc agc cct gct aag ctg atg atg ctg act ata gga gat gtt att aaa Leu Ser Pro Ala Lys Leu Met Met Leu Thr Ile Gly Asp Val Ile Lys 10 20 caa ctg att gaa gcc cac gag cag ggg aaa gac atc gat cta aat aag Gln Leu Ile Glu Ala His Glu Gln Gly Lys Asp Ile Asp Leu Asn Lys 25 30 35 40 gtg aga acc aag aca gct gcc aaa tat ggc ctt tct gcc cag ccc cgc Val Arg Thr Lys Thr Ala Ala Lys Tyr Gly Leu Ser Ala Gln Pro Arg 45 50 55 ctg gtg gat atc att gct gcc gtc cct cct gag tagctgggat tacaggcacc Leu Val Asp Ile Ile Ala Ala Val Pro Pro Glu 60 65 cgccgctgcc aatttttgta tttttagtag ggatggggt ttcaccatat tggtcaggct ggtctcgaac tcctgacctc aggtgatcaa cccaccttgg ctcccataa tggcaggatt acaggcatga gccaccgctc cgggcctttg atttttaag gtgggattttg gttgttataa atggagaaag gtaagagttc aagttcaacc cgtgtgtgaa agcaaaacaa tggaaaacag gattggcttc ttcaaaggct cctcttgtag aactgcctct tagaacttc gaggtaatct actttggaga ctctgcctgg agagggtcag ttcctaagtt aaaagcatcg cttaaccttg gctcctgtgg cattttacaa aggtttaaag gaattgattc ctctgaaag gcctgaaaat	102 150 198 251 311 371 431 491 551 611
Met Arg Gln Lys Arg Lys Gly Asp 1 5 ctc agc cct gct aag ctg atg atg ctg act ata gga gat gtt att aaa Leu Ser Pro Ala Lys Leu Met Met Leu Thr Ile Gly Asp Val Ile Lys 10 15 20 caa ctg att gaa gcc cac gag cag ggg aaa gac atc gat cta aat aag Gln Leu Ile Glu Ala His Glu Gln Gly Lys Asp Ile Asp Leu Asn Lys 25 30 35 40 gtg aga acc aag aca gct gcc aaa tat ggc ctt tct gcc cag ccc cgc Val Arg Thr Lys Thr Ala Ala Lys Tyr Gly Leu Ser Ala Gln Pro Arg 45 50 55 ctg gtg gat atc att gcc gcc gcc cct cct gag tagctggat tacaggcacc Leu Val Asp Ile Ile Ala Ala Val Pro Pro Glu 60 65 cgccgctgcc aattttgta tttttagtag ggatggggt ttcaccatat tggtcaggct ggtctcgaac tcctgacctc aggtgatcaa cccaccttgg cctccctaaa tggcggatt acaggcatga gccaccgctc cgggcctttg atttttaag ggtggttttg gttgttataa atggagaaag gtaagagttc aagttcaacc cgtgtgtgaa agcaaaacaa tggaaaacag gattggcttc ttcaaaggct cctcttgtag aactgcctct ttgaaatttc gaggtaatct actttggaga ctctqcctqq aqaqqqtcag ttcctaagtt aaaagcatcg cttaaccttg	102 150 198 251 311 371 431 491 551 611 671

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Cys Pro Thr Trp Gln Trp Ala Thr Gly Glu Glu Leu Lys Val Lys Ala
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                                                                       296
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 Glu Ser Gly Leu Leu Glu Thr Asp Glu Ala Thr Leu Asp Thr Arg Lys
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Lys	aaa Lys 185	aca Thr	gtg Val	acc Thr	att Ile	gaa Glu 190	aat Asn	cat His	cct Pro	cat His	ctg Leu 195	cca Pro	cca Pro	cct Pro	ccc Pro	824
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461 521 568

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Asn Ile Phe Pro Val Ile Ser Leu Tyr Leu Met Gly Glu Val Thr Asn
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                           230
       225
cag too tto ego ato acc ato ett eeg cag caa tae etg egg eca gtg
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Gln Ser Phe Arg Ile Thr Ile Leu Pro Gln Gln Tyr Leu Arg Pro Val
                                          250
                                                                   867
gaa gat gtg gcc acg tcc caa gac gac tgt tac aag ttt gcc atc tca
Glu Asp Val Ala Thr Ser Gln Asp Asp Cys Tyr Lys Phe Ala Ile Ser
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                   260
cag tca tcc acg ggc act gtt atg gga gct gtt atc atg gag ggc ttc
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Gln Ser Ser Thr Gly Thr Val Met Gly Ala Val Ile Met Glu Gly Phe
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Tyr Val Val Phe Asp Arg Ala Arg Lys Arg Ile Gly Phe Ala Val Ser
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Ala Cys His Val His Asp Glu Phe Arg Thr Ala Ala Val Glu Gly Pro
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Phe Cys His Leu Gly His Gly Arg Leu Trp Leu Gln His Ser Thr Asp
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                                                                  1112
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PYA
335
tettcatget gecaetetge etcatggtgt gtcagtggeg etgeeteege tgeetgegee
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cgggaaattc tgctgcttga aacttcagcc ctgaaccttt gtcaccattc ctttaaattc
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gccaaagtca gtaggagagg atgcacagtt tgctatttgc tttagagaca gggactgtat
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60

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-40
                           -45
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Ser Gly Ile Asp Leu Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu
                       -30
                                            -25
tta cct ttt gtg agt tta ggt ttg atg tgc ttt ggg gct ttg atc gga
Leu Pro Phe Val Ser Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly
                    -15
                                        -10
-20
                                                                      254
ctt tgt gct tgc att tgc cga agc tta tat ccc acc att gcc acg ggc
Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly
att ctc cat ctc ctt gca ggt ctg tgt aca ctg ggc tca gta agt tgt
                                                                     302
Ile Leu His Leu Leu Ala Gly Leu Cys Thr Leu Gly Ser Val Ser Cys
                            20
tat gtt gct gga att gaa cta ctc cac cag aaa cta gag ctc cct gac
                                                                      350
Tyr Val Ala Gly Ile Glu Leu Leu His Gln Lys Leu Glu Leu Pro Asp
                                            40
                                                                      398
aat gta too ggt gaa tit gga tgg too tio tgo cit got tgt gto tot
Asn Val Ser Gly Glu Phe Gly Trp Ser Phe Cys Leu Ala Cys Val Ser
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                    50
gct ccc tta cag ttc atg gct tct gct ctc ttc atc tgg gct gct cac
                                                                      446
Ala Pro Leu Gln Phe Met Ala Ser Ala Leu Phe Ile Trp Ala Ala His
                65
                                                                      491
acc aac cgg aga gag tac acc tta atg aag gca tat cgt gtg gca
Thr Asn Arg Arg Glu Tyr Thr Leu Met Lys Ala Tyr Arg Val Ala
                                85
                                                                      551
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                                                                      611
aatctatttt atttatacac attcaccact aaatacacac ttaataccac taaaatttat
                                                                      671
                                                                      731
gtggtttact ttaagcgatg ccatctttca aataaactaa tctaggtcta gacagaaaga
                                                                      791
aatggataga gacttgacac aaatttatga aagaaaattg ggagtaggaa tgtgaccgaa
aacaagttgt gctaatgtct gttagacttt tcagtaaaac caaagtaact gtatctgttc
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aactaaaaac tctatattag tttctttggg aaacctctca tcgtcaaaac tttatgttca
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tctgaggtga gatatggcag ctgtttgtat ctgcactgtg tctgtctaca aagagtgaaa
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aaagaacgtt tcaccataat gaccctccag agctgggaaa cctaccacaa gatctaaagt
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ttccttgcct aaatcccttc ctggtgtgta tcaacattat ttaatgtctt ctaattcagt
cattttttat aagtatgtct ataaacattg aactttaaaa aacttattta tttattccac
tactgtagca attgacagat taaaaaaatg taacttcata atttcttacc ataacctcaa
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<222> 69..287
<223> Von Heijne matrix
score 4
seq AVGFLFWVIVLTS/WI
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tgc cgg aag tac tac ctg ggg ggg ttt gct ttc ttg cct ttt ctc tgg Cys Arg Lys Tyr Tyr Leu Gly Gly Phe Ala Phe Leu Pro Phe Leu Trp -55 -50 -45	158
ttg gtc aac atc ttc tgg ttc tac cga gag gcc ttc ctt gtc cca gcc Leu Val Asn Ile Phe Trp Phe Tyr Arg Glu Ala Phe Leu Val Pro Ala -35 -30	206
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-50 -45 -40 agc cgc aac cct gag gtg ccc ttt gag agc agt gcc tac cgc atc tca	145

Ser	Arg	Asn	Pro	Glu	Val	Pro	Phe	Glu	Ser	Ser	Ala -25	Tyr	Arg	Ile	Ser .	
gct	tca	gcc	cgc	ggc	aag	gag	ctg	cgc	ctg	ata	ctg	agc	cct	ctg	cct	193
Ala	Ser	Ala	Arg	Gly	Lys	Glu	Leu	Arg	Leu	Ile	Leu	Ser	Pro	Leu	Pro	
-20	~~~	cad	cct	C = 2	-15	aaa	cca	cta	acc	-10	atc	ttc	cac	ttc	_	241
999 Glv	Ala	Gln	Pro	Gln	Gln	Glu	Pro	Leu	Ala	Leu	Val	Phe	Arg	Phe	Gly	
-				1				5					10			200
atg	tcc	ggc	tct	ttt	cag	ctg	gtg	CCC	cgc	gag	gag	ctg	cca	cgc	cat uie	289
Met	Ser	G1y	Ser	Pne	Gin	Leu	va1 20	PIO	Arg	GIU	GIU	25	FIO	AT 9	1115	
acc	cac	cta	cgc	ttt	tac	acg	qcc	ccg	cct	ggc	ccc	cgg	ctc	gcc	cta	337
Ala	His	Leu	Arg	Phe	Tyr	Thr	Ala	Pro	Pro	Gly	Pro	Arg	Leu	Ala	Leu	
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tgt	Dhe	gtg	gac Asp	atc	Ara	cgg Ara	Phe	Glv	Ara	Tro	Asp	Leu	Glv	Gly	Lys	500
45	Pne	vaı	Asp	116	50	A. 9	1 110		•••	55			1	•	60	
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Trp	Gln	Pro	Gly		Gly	Pro	Cys	Val	Leu	Gln	Glu	Tyr	Gln	Gln 75	Phe	
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agg	Glu	Asn	Val	Leu	Ara	Asn	Leu	Ala	Asp	Lys	Ala	Phe	Asp	Arg	Pro	
			80					85					90			
atc	tgc	gag	gcc	ctc	ctg	gac	cag	agg	ttc	ttc	aat	ggc	att	ggc	aac	529
Ile	Cys		Ala	Leu	Leu	Asp		Arg	Phe	Phe	Asn	Gly 105	Ile	СТУ	Asn	
		95	gca	~~~	atc	cta	100	caa	cta	aag	atc		ccc	ttt	gag	577
Tvr	Leu	Ara	Ala	Glu	Ile	Leu	Tyr	Arg	Leu	Lys	Ile	Pro	Pro	Phe	Glu	
	110					115					120					
aag	gcc	cgc	tcg	gtc	ctg	gag	gcc	ctg	cag	cag	cac	agg	ccg	agc	ccg	625
		Arg	Ser	Val		Glu	Ala	Leu	GIn	135	HIS	Arg	Pro	ser	140	
125	cta	acc	ctg	agc	130	aaq	ata	agg	acc		ctq	caq	aat	tca		673
Glu	Leu	Thr	Leu	Ser	Gln	Lys	Ile	Arg	Thr	Lys	Leu	Gln	Asn	Ser	Asp	
				145					150					155		77.1
ctg	ctg	gag	cta	tgt	cac	tca	gtg	CCC	aag	gaa	gtg	gtc	cag	Leu	ggt	721
Leu	Leu	Glu	Leu 160		HIS	ser	vai	165	гур	GIU	vaı	vai	170	Deu	Gly	
gag	acc	aaa	gat		agc	aac	ctc			agc	aaa	tga	ttgt	gta		767
Glu	Ala	Lys	Asp	ĞĨy	Ser	Asn	Leu	Cys	Phe	Ser	Lys					
		175					180							+ ~ + >	gggta	827
acc	ctgg	ggc	actt	gtcc	cc c	tctg	gacc	t ga	ctca	ccga	tat	ggaa	gtt	ctaa	gcccta	887
taa	gata	tac	ctat	gacu	eg g	gcac	ttca	ia da	gacc	gagt	qqq	qtqq	ctc	acct	gaggtc	947
agg	agtt	cqa	gacc	atco	tg g	ccaa	catg	g tg	aaac	ccca	tct	ccac	taa	aatg	caaaaa	1007
att	agco	agg	tqtq	qtqq	cg g	gcac	ctgt	a gt	ctca	gcta	. ctc	ggga	gga	tgag	gcagga	1067
aaa	tcgc	ttg	aacc	cagg	ag g	tgga	ggtt	g ca	gttg	agct	gag	atcg	tgc	catt	gcactc	1127 1174
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• •	
gac gct ttg cct cca agc aag gcc cct tcc aag aca cga agg gca aag Asp Ala Leu Pro Pro Ser Lys Ala Pro Ser Lys Thr Arg Arg Ala Lys	865
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ctc cag cag gac cca gaa gct ccc aca gtg ccc aag aag ggg agg agg Leu Gln Gln Asp Pro Glu Ala Pro Thr Val Pro Lys Lys Gly Arg Arg	961
240 245 250 aag ggg cga cag gcc tct ggc cac tgc aga ccc cgg aag gtc aag Lys Gly Arg Gln Ala Ala Ser Gly His Cys Arg Pro Arg Lys Val Lys	1009
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materialit transpage godaatatet qaaqqtqcaa acaggcccta cggctgttcc	1171
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-50 -45 -40 age ege aac cet gag gtg eec ttt gag age agt gee tae ege ate tea	145
Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Tie Ser	193
gct tca gcc cgc ggc aag gag ctg cgc ctg ata ctg agc cct ctg cct Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -20 -15 -10 -5	
ggg gcc cag ccc caa cag gag cca ctg gcc ctg gtc ttc cgc ttc ggc Gly Ala Gln Pro Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly	241
atg tcc ggc tct ttt cag ctg gtg ccc cgc gag gag ctg cca cgc cat Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 15 20 25	289

gcc c Ala H																337
tgt t		ata	~a~	2+6	cac		++-	aac	cac	taa		ctt	aaa	gga	aag	385
Cys P																303
tgg c	ag	ccg	ggc	cgc	ggg	ccc	tgt	gtc	ttg	cag	gag	tac	cag	cag	ttc	433
Trp G																
agg g	jag	aat	gtg	cta	cga	aac	cta	gcg	gat	aag	gcc	ttt	gac	cgg	CCC	481
Arg G			80		_			85	_	_			90			
atc t	_		_		_	_	_									529
Ile C	-	95				_	100					105				
tat c																577
_	10					115					120					625
aag g	icc	cgc	teg	gtc	ctg	gag	gcc	tou	cag	cag	Cac	agg	Dwa	age	Dro	623
Lys A	ııa	Arg	ser	vaı	130	GIU	AIA	теп	GIII	135	HIS	Arg	PLO	ser	140	
125 gag c				~~~		226	2+2	200	300		cta	C2C	22t	CC2		673
Glu L																0,5
GIUL	Jeu	THE	Leu	145	GIH	пуs	116	Arg	150	цуз	Leu	GIII	ASII	155	rop	
ctg c	ידמ	aaa	cta		cac	tca	ata	ccc		gaa	ata	atc	cad		aaa	721
Leu L																
DC4 2		014	160	Cys			•	165	_, _				170			
ggc a	ga	aac		aaa	tca	αaα	agc		gag	σаσ	gac	ttt		acc	ttt	769
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Met Leu Xaa Gly Asp His Arg Ala Leu Leu Leu 1 5 10 aag ata tgg ctg ctt caa agg cca gag tca cag gaa gga ctt ctt cca Lys Ile Trp Leu Leu Gln Arg Pro Glu Ser Gln Glu Gly Leu Leu Pro 15 20 25 ggg aga tta gtg gtg atg gag agg agg gtt aaa atg acc tca tgt cct Gly Arg Leu Val Val Met Glu Arg Arg Val Lys Met Thr Ser Cys Pro 30 35 40 tct tgt cca cgg ttt tgt tgagttttca ctcttctaat gcaagggtct Ser Cys Pro Arg Phe Cys 45 cacactgtga accacttagg atgtgatcac tttcaggtgg ccaggaatgt tgaatgtctt tggctcagtt catttaaaaa agatatctat ttgaaagttc tcagagttgt acatatgttt cacagtacag gatctgtaca taaaagttc tttcctaaac cattcaccaa gagccaatat ctaggcattt tcttggtagc acaaattttc ttattgctta gaaaattgtc ctccttgtta ttctgttgt taagacttaa gtgagttagg tctttaagg aagcaacgct cctctgaaat gctgtcttt tatgctgga ggtgaccata gggctctgct tttaaagaata tggctgcttc aaaggccaga gtcacaggaa ggacttcttc cagggagatt agtggtgatg gagaggagag	101 149 197 257 317 377 437 497 557 617 677 737
Met Leu Xaa Gly Asp His Arg Ala Leu Leu Leu 1 5 10  aag ata tgg ctg ctt caa agg cca gag tca cag gaa gga ctt ctt cca Lys Ile Trp Leu Leu Gln Arg Pro Glu Ser Gln Glu Gly Leu Leu Pro 15 20 25  ggg aga tta gtg gtg atg gag agg agg agg	101 149 197 257 317 377 437 497 557 617 677 737 797 857 917
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Met Léu Xaa Gly Asp His Arg Ala Leu Leu Leu 1 5 10 aag ata tgg ctg ctt caa agg cca gag tca cag gaa gga ctt ctc aca Lys Ile Trp Leu Leu Gln Arg Pro Glu Ser Gln Glu Gly Leu Leu Pro 15 20 25 ggg aga tta gtg gtg atg gag agg aga gtt aaa atg acc tca tgt cct Gly Arg Leu Val Val Met Glu Arg Arg Val Lys Met Thr Ser Cys Pro 30 35 40 tct tgt cca cgg ttt tgt tgagttttca ctcttctaat gcaagggtct Ser Cys Pro Arg Phe Cys 45 cacactgga accacttagg atgtgatcac tttcaggtgg ccaggaatgt tgaatgttt tggctcagtt catttaaaaa agatatctat ttgaaagttc tcagagttgt acatatgtt cacagtacag gatctgtaca taaaagttc tttctgtttg taagacttaa gtgagtagg tcttaaaga aggccaatat cttctgtttg taagacttaa gtgagtcagt tttattctgtttg taagacttaa gtgagtcag tcttaaaga aggccattt tcttggtag aggtgaccata gggcctctct tttaacaga ggccatat tggctgctc aaaggccaga gtcacaggaa ggacttcttc cagggagatt agtggtgat gggagagagg ttaaaatgac ctcatgtacc tcttgtcac ggttttgttg agtttcact cttctaatgc aagggccaca cactgtgaac cacttaggat gtgatcactt tcaggtggc aggagagag ttaaaatgac ctcatgtcct tcttgtccac ggttttgttg agttttcact cttctaatgc aagggcctca cactggaac cacttaggat gtgatcactt tcaggtggc aggagagag ttaaaatgctttg gctcagttca tttaaaaaaa atatctattt gaaagttct aaggttgtac atatgtttca cagtacagga tctgacaat aaggttcttc tcaggtggc aggaatgttg aatgtcttt tctgtttat tctgtttgta aaattttct tctaaacca ttcaccaaag gccaatatct aggcattttc ttggtagcac aaatttctt tctaaacca ttcaccaaaga gccaatatct aggcattttc ttggtagcac aaatttctt tctaaagaa aaatttctt tctgttatt tctgtttgta agacttaaagt gagttaggtc tttaaagaaa gcaacgctcc tctgaaatgc ttgtttatt tctgtttgta agacttaaagt gagttaggtc tttaaagaaa gcaacgctcc tctgaaatgc ttgtttatt tctgtttgta agacttaaagt gagttaggtc tttaaagaaa gcaacgctcc tctgaaatgc ttgttttaa gagcttaaagt gagttaggtc tttaaagaaa gcaacgctcc tctgaaatgc ttgtttatt tctgtttgta agacttaaag gagttaggt gagttagga gctctgctt taaagaaatgc ttgtttaaagaaagccacacacacacacacacacacacac	101 149 197 257 317 377 437 497 557 617 677 737 797 857 917 977
Met Leu Xaa Gly Asp His Arg Ala Leu Leu Leu 1 1 5 10 aag ata tgg ctg ctt caa agg cca gag tca cag gaa gga ctt ctt cca Lys Ile Trp Leu Leu Gln Arg Pro Glu Ser Gln Glu Gly Leu Leu Pro 15 20 25 ggg aga tta gtg gtg atg gag agg agg att aaa atg acc tca tgt cct Gly Arg Leu Val Val Met Glu Arg Arg Val Lys Met Thr Ser Cys Pro 30 35 40 tct tgt cca cgg ttt tgt tgagttttca ctcttctaat gcaagggtct Ser Cys Pro Arg Phe Cys 45 cacactgta accacttagg atgtgatcac tttcaggtgg ccaggaatgt tgaatgttt tgggtcagtt catttaaaaa agatactat ttgaaagttc tcaggatgt acatatgtt cacagtacag gatctgtaca taaaagttc tttcctaaac cattcaccaa gagccaatat ctaggcattt tcttggtag acaaattttc ttattgctta gaaaattgtc ctccttgtta ttctgtttg taagacttaa gtgagttagg tctttaagga aagcaacgct cctctgaaat gctgtcttt tatgctgga ggagtaccata gggctctgct tttaaagaat tggctgcttc aagaggtctc cacttaggac cacttaggat tctttgtcac ggagaggat tctttaacgaa ggagaggggtctca aagggccaga gtcacaaggaa tcttgtccac ggttttttt ggaacttct ccagggagat agtggtgatg gagaggagg tcaaaatgctct tattctgttt atgctgga ggacttct ccaggagatt tcttcacc cttctaatgc aagggtctca cacttggaac cacttaggat gtgatcactt tcaggtggc aggaaggagg cacatatct ggccaatatc aggccattct tctgtacac ggttttgtt gaagttctc atttaacaca tttaaaaaag atatctatt tcaggtggc aggaatgttg acatatgttc aatgtctt gccagttca tttaaaaaag atatctatt tcaggtggc aggaatgttgac atttatgttca cacttaggat tttaaaaaag atatctatt tcaggtggc aggattgtc atttaacaca tttaacaaga gccaatatct aggccatttc tcggtagca aaattttct attgcttaga aaattgcct ccttgtaatg tttgttatt tctgtttgta agacttaagt gagttaggtc tctaaaacca ttcacaaga gccaatatc tctgttagt agacttaagt gagttaggtc tctaaaggaa aacttcct cctgttaat tctgttaga agacttaagt gagttaggtc tctaaaaga aaatttcct tctgtaaatg ttgtctttaa gaccttaag gagttaggt tctaaaggaa gcaacgctcc tcttgaaatg ttgtctttaa gaccttaag gagttaggt tctaaaggaa gcaacgctcc tctgaaatg ttgtcttaa agacttaag gagttaggt gaccataag gcaacttct taaaggaaa gcaacgctcc tctgaaatg ttgtcttaa gacctaagg gagttaggag gagtgaggag gctcttaaatg gagttagga tcttaaaggaa gcaacgctcc tctgaaatg ttgtcttaa gagccaagg gagtgaggaggaggaggaggaggaggaggaggaggaggag	101 149 197 257 317 377 437 497 557 617 677 737 797 857 917 977 1037 1097
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Met Leu Xaa Gly Asp His Arg Ala Leu Leu Leu 1 1 5 10 aag ata tgg ctg ctt caa agg cca gag tca cag gaa gga ctt ctt cca Lys Ile Trp Leu Leu Gln Arg Pro Glu Ser Gln Glu Gly Leu Pro 15 20 25 ggg aga tta gtg gtg atg gag agg agg atg at	101 149 197 257 317 377 437 497 557 617 677 737 797 857 917 977 1037 1097 1157

1457 ...

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                                                        -25
aag ccg gtg tgg cca cgg cgc ttg gaa tcc tgg ttg ttg ctg gat gct
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Lys Pro Val Trp Pro Arg Arg Leu Glu Ser Trp Leu Leu Leu Asp Ala
                                                    -10
            -20
                                -15
ctt ttg cga tta gga gat acc aaa aaa aag cga cag cct gaa gca gcc
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Leu Leu Arg Leu Gly Asp Thr Lys Lys Lys Arg Gln Pro Glu Ala Ala
    -5
                           1
aca aaa too tgt gtt aga ago ago tgt ggg ggt coo agt gga gat ggg
                                                                     193
Thr Lys Ser Cys Val Arg Ser Ser Cys Gly Gly Pro Ser Gly Asp Gly
                    15
                                        20
cct ccc cca tgc ctc cag cag cct gac cct cgt gcc ctg tct cag gcg
                                                                     241
Pro Pro Pro Cys Leu Gln Gln Pro Asp Pro Arg Ala Leu Ser Gln Ala
ttc tct aga tcc ttt cct ctg ttt ccc tct ctc gct ggc aaa agt atg
                                                                     289
Phe Ser Arg Ser Phe Pro Leu Phe Pro Ser Leu Ala Gly Lys Ser Met
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ctc ttc ttc ttt ctc ttc ctc ctc acc agg ggc tca ctt tct cca aca Leu Phe Phe Phe Leu Phe Leu Thr Arg Gly Ser Leu Ser Pro Thr -10 -5 1 5	99
aaa tat aac ctt ttg gag ctc aag gag tct tgc atc cgg aac cag gac Lys Tyr Asn Leu Leu Glu Leu Lys Glu Ser Cys Ile Arg Asn Gln Asp 10 15 20	147
tgc gag act ggc tgc tgc caa cgt gct cca gac aat tgc gag tcg cac Cys Glu Thr Gly Cys Cys Gln Arg Ala Pro Asp Asn Cys Glu Ser His 25 30 35	195
tgc gcg gag aag ggg tcc gag ggc agt ctg tgt caa acg cag gtg ttc Cys Ala Glu Lys Gly Ser Glu Gly Ser Leu Cys Gln Thr Gln Val Phe 40 45 50	243
ttt ggc caa tat aga gcg tgt ccc tgc ctg cgg aac ctg act tgt ata Phe Gly Gln Tyr Arg Ala Cys Pro Cys Leu Arg Asn Leu Thr Cys Ile 55 60 65	291
tat tca aag aat gag aaa tgg ctt agc atc gcc tat ggc cgt tgt cag Tyr Ser Lys Asn Glu Lys Trp Leu Ser Ile Ala Tyr Gly Arg Cys Gln 70 75 80 85	339
aaa att gga agg cag aag ttg gct aag aaa atg ttc ttc tagtgctccc Lys Ile Gly Arg Gln Lys Leu Ala Lys Lys Met Phe 90 95	388
tccttcttgc tgcctcctcc tcctccacct gctctcctcc ctacccagag ctctgtgttc accctgttcc ccagagcctc caccatgagt ggagggaagt ggggagtgat tgaaataaag agctttttca atgaaaaaaa aaaaaaaaaa aaaa  <210> 79 <211> 233 <212> DNA <213> Homo sapiens  <220> <221> CDS	448 508 542
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att caa gta ttg aag atg ctg cca agg gaa aaa tta aga aga aga gaa Ile Gln Val Leu Lys Met Leu Pro Arg Glu Lys Leu Arg Arg Arg Glu 20 25 30	155
gag aga aaa caa ata aat ggg aaa aaa gaa agg aca aaa tat gaa aca Glu Arg Lys Gln Ile Asn Gly Lys Lys Glu Arg Thr Lys Tyr Glu Thr 35 40 45	203
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                         Met Val Ala Leu Asn Leu Ile Leu Val Pro
tgc tgc gct gct tgg tgt gac cca cgg agg atc cac tcc cag gat gac
                                                                      160
Cys Cys Ala Ala Trp Cys Asp Pro Arg Arg Ile His Ser Gln Asp Asp
                1
                                                                      208
gtg ccc cgt agc tct gct gct gat act ggg tct gcg atg cag cgg cgt
Val Pro Arg Ser Ser Ala Ala Asp Thr Gly Ser Ala Met Gln Arg Arg
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gag gcc tgg gct ggt tgg aga agg tca caa ccc ttc tct gtt ggt ctg
                                                                      256
Glu Ala Trp Ala Gly Trp Arg Arg Ser Gln Pro Phe Ser Val Gly Leu
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cct tct gct gaa aga ctc gag aac caa cca ggg aag ctg tcc tgg agg
                                                                      304
Pro Ser Ala Glu Arg Leu Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg
                                                             60
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                                       55
tcc ctg gtc gga gag gga tat aga atc tgt gac ctc tgacaactgt
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Ser Leu Val Gly Glu Gly Tyr Arg Ile Cys Asp Leu
                                    70
                65
gaagccaccc tgggctacag aaaccacagt cttcccagca attattacaa ttcttgaatt
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tgtctgtctg aggtgactta aaaaatcaga acaaaacttc tattatccag agtcatggga
                                                                      530
gagtacaccc tttccaggaa taatgttttg ggaaacactg aaatgaaatc ttcccagtat
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tgt ggc atg ccc ttg acc ctg ctt ggc ctg gct ttc tgc ctc cat cct

Cys Gly Met Pro Leu Thr Leu Leu Gly Leu Ala Phe Cys Leu His Pro

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ctg aca ata act gat gtt ccc gtc act gtt tat gca aca acg aga aag Leu Thr Ile Thr Asp Val Pro Val Thr Val Tyr Ala Thr Thr Arg Lys 20 25 30	249
cca cct gca caa agc agc aag gaa atg cat cct aaa tagcaccatt Pro Pro Ala Gln Ser Ser Lys Glu Met His Pro Lys 35 40 45	295
aagtettttg teaaggtetg aetaggteaa gggtaatgga eeagtateat etggtgatet ggtaaacaaa taaaagtggt ggeaeettea aaaaaaaaa a	355 396
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atg agg atg cag aga atc aag gtc tgt gag aag cga ccc agc ata gat Met Arg Met Gln Arg Ile Lys Val Cys Glu Lys Arg Pro Ser Ile Asp 10 15 20	147
cta tgc atc cac cac tgt tca tgt ttc caa aag tgt gaa aca aat aag Leu Cys Ile His His Cys Ser Cys Phe Gln Lys Cys Glu Thr Asn Lys 25 30 35	195
ata tgc tgt tca gcc ttc tgt ggg aac att tgt atg agc atc cta Ile Cys Cys Ser Ala Phe Cys Gly Asn Ile Cys Met Ser Ile Leu 40 45 50	240

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Lys	Leu 10	Phe	Asp	Ala	Pro	Leu 15	Ser	Ile	Ser	Lys	Arg 20	Glu	Gln	Leu	Glu	
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Gln 25	Gln	Val	Pro	Glu	Asn 30	Tyr	Phe	Tyr	Val	Pro	Asp	Leu	Gly	Gln	Val 40	
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Asn	Asp	Leu	Met 60	Tyr	Ile	Ala	Asp	Leu 65	GIY	Pro	GIY	Ile	Ala 70	Pro	Ser	
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Ala	Pro	G1y 75	Thr	Ile	Pro	Glu	Leu 80	Pro	Thr	Phe	His	Thr	Glu	Val	Ala	
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-20

-15

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Leu Glu His Thr Pro Leu Asp Phe Leu Glu Trp Gly Leu Leu Arg	
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321

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WO 99/31236 -70- PCT/IB98/02122

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Gly	Ile		Tyr	Tyr	Leu	Met		Pro	Ser	Leu	Gln	Val	Ser	GIn	GIA	
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Lys		His	Ser	Leu	Val		Pro	Ser	Val	Asp		vaı	Cys	GIN	Leu	
	160					165			.		170	~~+	-	~~~	ast	729
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Tou	TON	37-1	Dic	Trn	Cys	Wie	GJV	בומ	Pro	SIV	Val	Tle	Tvr	Met	Leu	
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Tle	Gln	Ala	Tvr	Lvs	Val	Phe	Ara	Glu	Glu	Lvs	Tyr	Leu	Cys	Asp	Ala	
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Tyr	Gly	Leu	Cys	His	Gly	Ser	Ala	Gly	Asn	Ala		Ala	Phe	Leu	Thr	
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yac	The	DTO	Dhe	Cor	Leu	Dhe	Glu	Glv	Met	Δla	Glv	Thr	Ile	Tvr	Phe	
Asp	1111	PIO	290	261	пец	FIIC	OIU	295			<b>-</b> 1		300	-7-		
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Leu	Ala	Asp	Leu	Leu	Val	Pro	Thr	Lys	Ala	Arg	Phe	Pro	Ala	Phe	Glu	
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Leu																
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gaa aaa cac a Glu Lys His T 10 aca aaa aaa a Thr Lys Lys L	hr His Thr Hi 15 aa aaa a	1 c aca cat ata	5 a cac aca cac a e His Thr His T 20	ıca cga aaa	401
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Cys Gln Arg Arg Trp Pro Asp Arg Cys Leu Gln Ser His Thr Gln 35 40 45	
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act gag atg cct cta aga gcc aaa gga gtc aac act tgagcctagg Thr Glu Met Pro Leu Arg Ala Lys Gly Val Asn Thr 10 15	304
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Met Glu Leu Ala Pro Thr Ala Arg Leu Pro Pro Gly His Gly Ser  1 5 10 15  ttg ccc cat ggt gtc ctg gga ccc aga gca aca gga tct gtc acc cac Leu Pro His Gly Val Leu Gly Pro Arg Ala Thr Gly Ser Val Thr His  20 25 30  ctc tct ctt ctc ccc cag atc aag caa cgt gcc tca gag gct ttg ccc Leu Ser Leu Leu Pro Gln Ile Lys Gln Arg Ala Ser Glu Ala Leu Pro  35 40 45  gaa ttg ctt cgt cct gtc acc ccc atc acc aat ttt gag ggc agc cag Glu Leu Leu Arg Pro Val Thr Pro Ile Thr Asn Phe Glu Gly Ser Gln  50 55 60  ctc cag gac cac agt gga atc ttt ggc ctg gta aca aac ctg gaa gag Ser Gln Asp His Ser Gly Ile Phe Gly Leu Val Thr Asn Leu Glu Glu  65 70 75  ctg gag gtg gac gat tgg gag ttc tgagcctctg caaactgtgc gcattctca Leu Glu Val Asp Asp Trp Glu Phe 80 85  gccagggatg cagaggccac ccagaggccc ttcctgaggg ccggccacat tcccgcctc ctgggcagat tgggtagaaa ggacattctt ccaggaaagt tgagtgctgg ctgattgga aagaaaatcc tggagagata cttcactgct ccaaggcttt tgagacacaa gggaatctca acaaccaggg atcaggaggg tccaaagccg acattcccag tcctgtagc tcaggtgacc tcctccgcag aagaggatg ctgctctggc cctgggagct gaattccaag cccagggttt	110 158 206 254 302 356 416 476 536 596 656
Met Glu Leu Ala Pro Thr Ala Arg Leu Pro Pro Gly His Gly Ser  1 5 10 15  ttg ccc cat ggt gtc ctg gga ccc aga gca aca gga tct gtc acc cac Leu Pro His Gly Val Leu Gly Pro Arg Ala Thr Gly Ser Val Thr His  20 25 30  ctc tct ctt ctc ccc cag atc aag caa cgt gcc tca gag gct ttg ccc Leu Ser Leu Leu Pro Gln Ile Lys Gln Arg Ala Ser Glu Ala Leu Pro  35 40 45  gaa ttg ctt cgt cct gtc acc ccc atc acc aat ttt gag ggc agc cag Glu Leu Leu Arg Pro Val Thr Pro Ile Thr Asn Phe Glu Gly Ser Gln  50 55 60  tct cag gac cac agt gga atc ttt ggc ctg gta aca acc ctg gaa gag Ser Gln Asp His Ser Gly Ile Phe Gly Leu Val Thr Asn Leu Glu Glu  65 70 75  ctg gag gtg gac gat tgg gag ttc tgagcctctg caaactgtgc gcattctcca Leu Glu Val Asp Asp Trp Glu Phe  80 85  gccagggatg cagaggccac ccagaggccc ttcctgaggg ccggccacat tcccgccctc ctgggcagat tgggtagaaa ggacattctt ccaggaaagt tgactgtgg ctgattgga aagaaaatcc tggagagata ctccaatgcc acatcccag tcctgtgagc tcagtggac ctcatcagg accacagaggac cccagaggct tcccaggagct gaattccaa gcacacagg atcaggaggt ccaaaagccg acattcccag tcctgtgagc tcagtgtgac ctcctccgcag aagagagat ctgctctggc cctgggagct gaattccaag cccagggttt ggctccttaa acccgaggac cgccacctct tcccagtgct tgcgaccagc ctcattctac	110 158 206 254 302 356 416 476 536 596
Ctctc atg gag ttg gct ccg aca gcc cgt ctg cca cca ggc cat ggt tcc  Met Glu Leu Ala Pro Thr Ala Arg Leu Pro Pro Gly His Gly Ser  1 5 10 15  ttg ccc cat ggt gtc ctg gga ccc aga gca aca gga tct gtc acc cac  Leu Pro His Gly Val Leu Gly Pro Arg Ala Thr Gly Ser Val Thr His  20 25 30  ctc tct ctt ctc ccc cag atc aag caa cgt gcc tca gag gct ttg ccc  Leu Ser Leu Leu Pro Gln Ile Lys Gln Arg Ala Ser Glu Ala Leu Pro  35 40 45  gaa ttg ctt cgt cct gtc acc ccc atc acc aat ttt gag ggc agc cag  Glu Leu Leu Arg Pro Val Thr Pro Ile Thr Asn Phe Glu Gly Ser Gln  50 55 60  tct cag gac cac agt gga atc ttt ggc ctg gta aca aac ctg gaa gag  Ser Gln Asp His Ser Gly Ile Phe Gly Leu Val Thr Asn Leu Glu Glu  65 70 75  ctg gag gtg gac gat tgg gag ttc tgagcctctg caaactgtgc gcattctcca  Leu Glu Val Asp Asp Trp Glu Phe  80 85  gccagggatg cagaggccac ccagaggccc ttcctgaggg ccggccacat tcccgccctc  ctgggcagat tgggtagaaa ggacattctt ccaggaaagt tgactgctgg ctgattgga  aagaaaatcc tggagagata cttcactgct ccaaggcttt tgagacacaa gggaatcca  accaccaggg atcagaggt ccaaaagccg acattcccag tcctgtgagc tcaggtacc  tcctcccgcag aagaggatg ccgcacctct tcccaggagct gaattccaag cccagggttt  ggctccttaa acccgaggac cgccacctct tcccagtgct tgcgaccagc ctcattctac  ttaactttgc tctcagatgc ctcagatgct ataggtcagt gaaagggcga gtagtaagct	110 158 206 254 302 356 416 476 536 596 656 716
Met Glu Leu Ala Pro Thr Ala Arg Leu Pro Pro Gly His Gly Ser  1	110 158 206 254 302 356 416 476 536 596 656 716 776 836 896
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Ser Ser Ser Leu Arg Leu Thr Arg Ser Ser Asp Leu Lys Arg Ile Asn

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aaa Lys	Ala	30 aga Arg	ttt Phe	gat Asp	cca Pro	Tyr	35 gga Gly	aag Lys	aat Asn	aag Lys	ttc Phe 55	40 tcc Ser	act Thr	tgt Cys	aga Arg	194
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	cca	900	cac	ata		cad	caa	cta	gat		acc	cga	+++	cgc		829
Tou	7×~	77.	720	Mot	אות	Cln	722	Len	) en	222	200	Ara	Dhe	Arg	Tur	
				220					225					230		
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Leu		Leu	Gln	Pro	Cys		Tyr	Lys	Arg	Arg						
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aga	a++ :	+ > 0	-5	<b>~</b>	act	G a C	aad		tac	ato	tta	_	gaa	tat	acq	147
Arg	Leu '	Tur	His	Glu	Δla	Asp	Lvs	Thr	Tvr	Met	Leu	Arq	Glu	Tyr	Thr	
	10	- y +	1110	<u></u>		15	-1-		-1-		20			-		
tca	cga	gaa	aqc	aaa	att	tct	agt	ttg	atg	cat	gtt	cca	cct	tcc	ctc	195
Ser	Arg	Glu	Ser	Lys	Ile	Ser	Ser	Leu	Met	His	Val	Pro	Pro	Ser	Leu	
25					30					35					40	
ttc	acg	gaa	cct	aat	gaa	ata	tcc	cag	tat	tta	cca	ata	aag	gaa	gca	243
Phe	Thr	Glu	Pro	Asn	Glu	Ile	Ser	Gln	Tyr	Leu	Pro	Ile	Lys	Glu	Ala	
				45					50					55		201
gtt	tgt	gag	aag	cta	ata	ttt	cca	gaa	aga	att	gat	cct	aac	cca	gca	291
Val	Cys	Glu		Leu	Ile.	Phe	Pro		Arg	Ile	Asp	Pro	Asn	Pro	Ala	
			60					65					70	a <del>t-</del>		338
gac	tca	caa	aaa	agt	aca	caa	gtg	gaa	taa	aatg	tga	Laca	acat	ac		330
Asp	Ser	75	гåг	ser	Inr	GIII	80	GIU								
acto	·acta		722 <b>+</b> 0	-+	-t a	raca.		a ac	tatt	tata	agg	aatt	att	ttta	ttatga	398
gest	.accd	to 1	ctte	ya	at of	taca	gatt	t to	tota	acct	taa	agga	aaa	aaaa	ataaag	458
	ttac															494
4005	, Luau	~= 5	,9:	, '		~										

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<222> 84..332

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taccettgag tgatgtgeet tga atg acg etg ett tea tte get get tte acg
                                                                  113
                         Met Thr Leu Leu Ser Phe Ala Ala Phe Thr
                                                                  161
get get tte tee gte etc ecc tgt tae tae ett ggg etg ttt eag egg
Ala Ala Phe Ser Val Leu Pro Cys Tyr Tyr Leu Gly Leu Phe Gln Arg
                                  -10
               -15
                                                                  209
gcg ctc gcg tcg gtc ttc gac cca ctt tgc gtt tgt tca cgt gtg ctc
Ala Leu Ala Ser Val Phe Asp Pro Leu Cys Val Cys Ser Arg Val Leu
                                              10
           1
ccg aca cct gta tgt acc ttg gtc gca aca caa gcc gaa aaa ata tta
                                                                  257
Pro Thr Pro Val Cys Thr Leu Val Ala Thr Gln Ala Glu Lys Ile Leu
                       20
                                          25
gag aat ggg ccc tgt cca acc aag gag gcg gcc cag ctt gtc ggg aag
                                                                  305
Glu Asn Gly Pro Cys Pro Thr Lys Glu Ala Ala Gln Leu Val Gly Lys
                                                          4.5
                   35
                                      40
                                                                  352
ggc agc gtt tcc gcc aga aat gct tcg tgaaaggcac ttgagggacc
Gly Ser Val Ser Ala Arg Asn Ala Ser
               50
ttagcagcat cctcaacagg ccttgtaggg aatgccagaa gaagcagtcc ttggccgggc
                                                                  412
ggggtggctc atgcctgtgg tcccagcact ttgggaggcc ggggcgggcg gatcacctga
                                                                  472
ggtcgggagg tccagaccag cctgaccgac atggagaaac cccgtctnta ctagaaatac
                                                                  532
                                                                  592
aaaactagcc gggtgtggtg gcgcatgcct gtagtcccag ctactcggga gggtgaggca
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712
                                                                   714
aa
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<213> Homo sapiens

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<222> 32..718

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<222> 32..100
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score 7.4
seq VLLLAALPPVLLP/GA

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<221> polyA_site

<222> 793..805

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ggg gcg gcc ggc ttc aca cct tcc ctc gat agc gac ttc acc ttt acc Gly Ala Ala Gly Phe Thr Pro Ser Leu Asp Ser Asp Phe Thr Phe Thr 1 5 10 15	148
ctt ccc gcc ggc cag aag gag tgc ttc tac cag ccc atg ccc ctg aag Leu Pro Ala Gly Gln Lys Glu Cys Phe Tyr Gln Pro Met Pro Leu Lys 20 25 30	196
gcc tcg ctg gag atc gag tac caa gtt tta gat gga gca gga tta gat Ala Ser Leu Glu Ile Glu Tyr Gln Val Leu Asp Gly Ala Gly Leu Asp 35 40 45	244
att gat ttc cat ctt gcc tct cca gaa ggc aaa acc tta gtt ttt gaa Ile Asp Phe His Leu Ala Ser Pro Glu Gly Lys Thr Leu Val Phe Glu 50 55 60	292
caa aga aaa tca gat gga gtt cac act gta gag act gaa gtt ggt gat Gln Arg Lys Ser Asp Gly Val His Thr Val Glu Thr Glu Val Gly Asp 65 70 75 80	340
tac atg ttc tgc ttt gac aat aca ttc agc acc att tct gag aag gtg Tyr Met Phe Cys Phe Asp Asn Thr Phe Ser Thr Ile Ser Glu Lys Val 85 90 95	388
att ttc ttt gaa tta atc ctg gat aat atg gga gaa cag gca caa gaa Ile Phe Phe Glu Leu Ile Leu Asp Asn Met Gly Glu Gln Ala Gln Glu 100 105 110	436
caa gaa gat tgg aag aaa tat att act ggc aca gat ata ttg gat atg Gln Glu Asp Trp Lys Lys Tyr Ile Thr Gly Thr Asp Ile Leu Asp Met 115 120 125	484
aaa ctg gaa gac atc ctg gaa tcc atc agc agc atc aag tcc aga cta Lys Leu Glu Asp Ile Leu Glu Ser Ile Ser Ser Ile Lys Ser Arg Leu 130 135 140	532
agc aaa agt ggg cac ata caa att ctg ctt aga gca ttt gaa gct cgt Ser Lys Ser Gly His Ile Gln Ile Leu Leu Arg Ala Phe Glu Ala Arg 145 150 155	580
gat cga aac ata caa gaa agc aac ttt gat aga gtc aat ttc tgg tct Asp Arg Asn Ile Gln Glu Ser Asn Phe Asp Arg Val Asn Phe Trp Ser 165 170 175	628
atg gtt aat tta gtg gtc atg gtg gtg tca gcc att caa gtt tat Met Val Asn Leu Val Val Met Val Val Val Ser Ala Ile Gln Val Tyr 180 185 190	676
atg ctg aag agt ctg ttt gaa gat aag agg aaa agt aga act Met Leu Lys Ser Leu Phe Glu Asp Lys Arg Lys Ser Arg Thr 195 200 205	718
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<222> 26..481

<221> sig_peptide

<222> 26..88

<223> Von Heijne matrix

score 4.4 seq AVASSFFCASLFS/AV

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ata	gct	tcc	agt	ttc	ttt	tgt	gca	tct	ctc	ttc	tca	gct	gtg	cac	aag	100
Val	Āla	Ser	Ser	Phe	Phe	Cys	Āla	Ser	Leu	Phe	Ser	Ala	Val	His	Lys	
		-10				-	-5					1				
ata	gaa	gag	gga	cat	att	aaa	qta	tat	tac	aqa	qqc	qqt	gcc	ctg	ctg	148
			Gly													
5			1		10	1		- 4 -	-1-	15		•			20	
	tca	acc	agc	aac		aat	ttc	cat	ctc	atq	ctc	cct	ttc	atc	aca	196
Thr	Ser	Thr	Ser	Glv	Pro	Glv	Phe	His	Leu	Met	Leu	Pro	Phe	Ile	Thr	
1111	001		001	25		<b>U</b> +1			30					35		
tca	tat	aad	tct		cad	acc	aca	ctc		aca	gat	gag	ata	aaq	aat	244
			Ser													
361	TYL	цуs	40	vai	GIII	1111		45	0111			014	50	275		
~		+~+	999	20+	205	aat	aat		ata	ato	tac	+++		aga	att	292
yca wal	Dwo	Cyc.	Gly	The	cor	990	990	Val	Mot	Tla	Tyr	Dhe	Den	Ara	Tle	
vai	PIO	55	GIY	IIII	ser	Gry	60 60	VAI	MEC	116	- Y -	65	ASP	AT 9		
									~~~	~+~	a = +		2+2	a+a	220	340
gaa	gtg	grg	aac	בנכ	ctg	gee	Des	aac	gca	gra	Uac	yar.	Tla	77-1	Larg	340
GIU		val	Asn	Pne	Leu		PIO	ASII	Ald	vai	80	Asp	TIE	vai	шys	
	70					75		·							~~~	388
aac	tat	act	gct	gac	tat	gac	aag	gcc	CLC	alc	משט	aac	aag	Tlo	Uic	300
	Tyr	Thr	Ala	Asp	_	Asp	гÀг	Ala	Leu		Pne	ASI	тÀг	116	100	
85					90					95						436
cac	gaa	ctg	aac	cag	ttc	tgc	agt	gtg	cac	acg	ctt	caa	gag	gtc	tac	436
His	Glu	Leu	Asn		Phe	Cys	Ser	Val		Thr	Leu	GIn	GIU		Tyr	
				105					110					115		
att	gag	ctg	ttt	gga	ctg	gaa	aat	gat	ttt	tcc	cag	gaa	tct	tca		481
Ile	Glu	Leu	Phe	Gly	Leu	Glu	Asn		Phe	Ser	Gln	Glu		Ser		
			120					125					130			
															catcgc	541
															atccaa	601
															ttgtag	661
															cgttga	721
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<222> 26..187

<223> Von Heijne matrix score 4.1

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tct tcg ccg Ser Ser Pro	tct ttg aaa aca Ser Leu Lys Thr -40	gac aca tcc Asp Thr Ser	cct gtc ctt gaa	act gca 100 Thr Ala
gga acg gto	gca gca atg gct Ala Ala Met Ala -25	gcg acc ccg Ala Thr Pro -20	tca gca agg gct Ser Ala Arg Ala	gca gcc 148 Ala Ala -15
gcg gtg gtt Ala Val Val	gcg gcc gcg gcc Ala Ala Ala Ala -10	agg acc gga Arg Thr Gly -5	tcc gaa gcc agg Ser Glu Ala Arg	ggtc tcc 196 g Val Ser
aag gcc gct Lys Ala Ala 5	ttg gct acc aag Leu Ala Thr Lys	ctg ctg tcc Leu Leu Ser	ttg agc ggc gtg Leu Ser Gly Val	ttc gcc 244 Phe Ala
gtg cac aag Val His Lys 20	ccc aaa ggg ccc Pro Lys Gly Pro 25	act tca gcc Thr Ser Ala	gag ctg ctg aat Glu Leu Leu Asr 30	cgg ttg 292 Arg Leu 35
	ctg ctg gca gaa Leu Leu Ala Glu 40			
	aag cag act ttg Lys Gln Thr Leu 55			
agc gca gcc Ser Ala Ala 70	cga gga gtt ctg Arg Gly Val Leu	gtt gtt gga Val Val Gly 75	att gga agc gga Ile Gly Ser Gly 80	aca aaa 436 Thr Lys
atg ttg acc	agt atg ttg tca Ser Met Leu Ser 90	ggg tcc aag		
gaa ctg ggg	aaa gct act gat Lys Ala Thr Asp 105			
gaa gaa aaa	cct tac ggt atg Pro Tyr Gly Met 120		taagtag	569

<210> 113

<211> 893

<212> DNA

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<221> CDS

<222> 4..810

<221> sig_peptide

<222> 4..279

<223> Von Heijne matrix score 6.8 seq AVMLYTWRSCSRA/IP

<221> polyA_signal

<222> 858..863

<221> polyA_site <222> 881..893

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:tg	ctt	gaa	gag	ctt	ccc	ctc	ccc	gac	cag	cag	cca	tgc	atc	gag	cct	9
eu	Leu	Glu -75	Glu	Leu	Pro	Leu	Pro -70	Asp	Gln	Gln	Pro	Cys -65	Ile	Glu	Pro	
ca	cct	tcc	tcc	atc	atg	tac	cag	gct	aac	ttt	gac	aca	aac	ttt	gag	14
	-60			Ile		-55					-50					19
gac	agg	aat	gca	ttt Phe	gtc	acg	ggc	att	gca Ala	agg	Tvr	att Tle	gag Glu	Gln	Ala	19
45p	Arg	ASII	VIG	FIIC	-40	1111	Cly			-35	- , -				-30	
aca	gtc	cac	tcc	agc	atg	aat	gag	atg	ctg	gag	gaa	gga	cat	gag	tat	24
				Ser -25					-20					-15		
gcg	gtc	atg	ctg	tac	acc	tgg	cgc	agc	tgt	tcc	cgg	gcc	att	CCC	cag	28
			-10	Tyr				-5					1			
gtg	aaa	tgc	aac	gag	cag	CCC	aac	cga	gta	gag	atc	tat	gag	aag	aca	33
	5	-		Glu		10					15			•		2.0
gta	gag	gtg	ctg	gag Glu	ccg	gag	gtc	acc	aag	ctc	atg	aag	Dhe	atg	Tur	31
vaı 20	GIU	vaı	ren	GIU	25	GIU	vaı	1111	пуз	30	Mec	Буз	rnc		35	
tt	cag	cgc	aag	gcc	atc	gag	cgg	ttc	tgc	agc	gag	gtg	aag	cgg	ctg	4:
		_	_	Ala 40					45					50		
tgc	cat	gcc	gag	cgc	agg	aag	gac	ttt	gtc	tct	gag	gcc	tac	ctc	ctg	4
			55	Arg				60					65			_
200	ctt	ggc	aag	ttc Phe	atc	aac	atg	ttt	gct	gtc	ctg	gat	gag	Leu	aag Lvs	5
		70					75					80				
aac	atg	aag	tgc	agc	gtc	aag	aat	gac	cac	tcc	gcc	tac	aag	agg	gca	5
	85			Ser		90					95					
gca	cag	ttc	ctg	cgg	aag	atg	gca	gat	CCC	cag	tct	atc	cag	gag	tcg	6
	Gln	Phe	Leu	Arg	Lys 105	Met	Ala	Asp	Pro	110	ser	TIE	GIN	GIU	115	
100 cag	aac	ctt	tcc	atg		ctq	qcc	aac	cac		agg	atc	acc	cag		6
Gln	Asn	Leu	Ser	Met 120	Phe	Leu	Ala	Asn	His 125	Asn	Arg	Ile	Thr	Gln 130	Cys	
ctc	cac	cag	caa	ctt	gaa	gtg	atc	cca	ggc	tat	gag	gag	ctg	ctg	gct	7
			135					140					145		Ala	
gac	att	gtc	aac	atc	tgt	gtg	gat	tac	tac	gag	aac	aag	atg	tac	ctg	7
_		150					155					160			Leu	
act	ccc	agt	gag	aaa	cat	atg	cto	ctc	aag	gta	aaa	ctc	CCC			ε
Thr			Glu	Lys	His	Met		Leu	гÀг	val	Lys 175		Pro	•		
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<223> Von Heijne matrix
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<221> polyA_signal
<222> 1444..1449
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<222> 1462..1475
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Gln Thr Val Tyr Tyr Gly Ser Leu Gly Leu Trp Leu Ala Leu Val Asp
                                           -10
                                                                    153
ggg cta gtg cga agc agc ccc tcg ctg gac cag atg ttc gac gcc gag
Gly Leu Val Arg Ser Ser Pro Ser Leu Asp Gln Met Phe Asp Ala Glu
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                                   5
                                                                    201
atc ctg ggc ttt tcc acc cct cca ggc cgg ctc tcc atg atg tcc ttc
Ile Leu Gly Phe Ser Thr Pro Pro Gly Arg Leu Ser Met Met Ser Phe
                               20
            15
atc ttc aac gcc ctc acc tgt gcc ctg ggc ttg ctg tac ttc atc cgg
                                                                    249
Ile Phe Asn Ala Leu Thr Cys Ala Leu Gly Leu Leu Tyr Phe Ile Arg
                                               40
                           35
cga gga aag cag tgt ctg gat ttc act gtc act gtc cat ttc ttt cac
                                                                    297
Arg Gly Lys Gln Cys Leu Asp Phe Thr Val Thr Val His Phe Phe His
                       50
ctc ctg ggc tgc tgg ttc tac agc tcc cgt ttc ccc tcg gcg ctg acc
                                                                    345
Leu Leu Gly Cys Trp Phe Tyr Ser Ser Arg Phe Pro Ser Ala Leu Thr
                    65
tgg tgg ctg gtc caa gcc gtg tgc att gca ctc atg gct gtc atc ggg
                                                                    393
Trp Trp Leu Val Gln Ala Val Cys Ile Ala Leu Met Ala Val Ile Gly
                                    85
                                                                     441
gag tac ctg tgc atg cgg acg gag ctc aag gag ata ccc ctc aac tca
Glu Tyr Leu Cys Met Arg Thr Glu Leu Lys Glu Ile Pro Leu Asn Ser
                                100
            95
gcc cct aaa tcc aat gtc tagaatcagg ccctttggac atcccgctga
                                                                     489
Ala Pro Lys Ser Asn Val
        110
                                                                    549
cacttgggcc ccttaacacc ttgggctgct cagaccctcc agatgaggtc cagcccagat
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ctgagaggaa ccctggaaat gtgaagtctc tgttggtgtg ggagagatag tgagggcctg
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ccttggtatc tgagaggtca ggaaggggac ctctttgagg gtaataacat aattggaacc
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caaggatatc tgattggagc aaaccacttc tttagtcatc tgtcttacct ccctgggaca
                                                                     849
gctgttacct ttgcagtgtt gccgaatcac agcagttacc tttgcaatgt tgccgaatca
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                                                                    1029
                                                                    1089
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                                                                    1149
                                                                    1209
taggacccag agaagaatcc cagtgttgct caaagtctga ccatcataaa gacactgcct
                                                                    1269
gtottotagg aatgaccagg cacccagoto coactggact coaattttt ttoctgoott
                                                                    1329
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ctggcctggg ctgtgctgat agtgctgagg gagataggaa tttgctgcta agatttttct
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<222> 48..161
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<222> 283..288
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<222> 308..321
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gtg cag ccg aaa ata aaa cat cgc ccc ttc tgc ttc agt gtg aaa ggc
                                                                      104
Val Gln Pro Lys Ile Lys His Arg Pro Phe Cys Phe Ser Val Lys Gly
                                                            -20
                    -30
                                        -25
-35
                                                                      152
cac gtg aag atg ctg cgg ctg gtg ttt gca ctt gtg aca gca gta tgc
His Val Lys Met Leu Arg Leu Val Phe Ala Leu Val Thr Ala Val Cys
                -15
                                     -10
                                                                      200
tgt ctt gcc gac ggg gcc ctt att tac cgg aag ctt ctg ttc aat ccc
Cys Leu Ala Asp Gly Ala Leu Ile Tyr Arg Lys Leu Leu Phe Asn Pro
aac ggt cct tac cag aaa aag cct gtg cat gaa aaa aaa gaa gtt ttg
                                                                      24B
Asn Gly Pro Tyr Gln Lys Lys Pro Val His Glu Lys Lys Glu Val Leu
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aaaaaaaaa aaa
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seq SILAQVLDQSARA/RL

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agg aga cag agg ctg gcc gag ctg cag gcc aaa cac ggg gat cct gg Arg Arg Gln Arg Leu Ala Glu Leu Gln Ala Lys His Gly Asp Pro Gl -45 -40 -35	- y 10
gat gcg gcc caa cag gaa gca aag cac agg gaa gca gaa atg aga aa Asp Ala Ala Gln Gln Glu Ala Lys His Arg Glu Ala Glu Met Arg As -25 -20 -15	sn
agt atc tta gcc caa gtt ctg gat cag tcg gcc cgg gcc agg tta ag Ser Ile Leu Ala Gln Val Leu Asp Gln Ser Ala Arg Ala Arg Leu Se -10 -5 1	gt 195 er
aac tta gca ctt gta aag cct gaa aaa act aaa gca gta gag aat ta Asn Leu Ala Leu Val Lys Pro Glu Lys Thr Lys Ala Val Glu Asn Ty 5 10 15	nc 243 vr
ctt ata cag atg gca aga tat gga caa cta agt gag aag gta tca ga Leu Ile Gln Met Ala Arg Tyr Gly Gln Leu Ser Glu Lys Val Ser Gl 20 25 30 35	lu
caa ggt tta ata gaa atc ctt aaa aaa gta agc caa caa aca gaa aa Gln Gly Leu Ile Glu Ile Leu Lys Lys Val Ser Gln Gln Thr Glu Ly 40 45 50	ag 339 /s
aca aca aca gtg aaa ttc aac aga aga aaa gta atg gac tct gat ga Thr Thr Thr Val Lys Phe Asn Arg Arg Lys Val Met Asp Ser Asp Gl	aa 387 lu
gat gac gat tat tgaactacaa gtgctcacag actagaactt aacggaacaa Asp Asp Asp Tyr 70	439
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Arg Lys Gly Thr His Lys Asp Val Leu Glu Glu Gly Thr Glu Ser Ser

tee cae tee agg etg tee eec ega aag ace cae tta etg tae ate etc

150

155

638

686

130

Ser His Ser Arg Leu Ser Pro Arg Lys Thr His Leu Leu Tyr Ile Leu 160 165 170 175	5 24
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            -30
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        -15
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 Ser Thr
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395

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Trp Gly Ala Glu Lys Gly Glu Ser Pro Glu Val Ser Ser Phe Glu Thr
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ace ttt tte daa ata tagteactet etgaggtaet gatggttagg ateteaacat Thr Phe Phe Gln Ile 35	271
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1 5 10 15 gaa ccc ccg ctc ttg ctt ggt gtt ctg cat cca aat acg aag ctg cga	265
Glu Pro Pro Leu Leu Gly Val Leu His Pro Asn Thr Lys Leu Arg 20 25 30	
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Gly	Pro	Cys	Lys		Arg	Asp	Asp	Glu		Val	Cys	Gly	Arg		Leu	
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Lys	Gly		Phe	Glu	Val	Asn		Trp	Lys	Arg	Glu	Val	Lys	Leu	Leu	
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Phe Arg Lys Asn Lys Thr Leu Gly Tyr Gly Val Pro Met Leu Leu Leu
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                                                    -10
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Ile Val Gly Sly Ser Phe Gly Leu Arg Glu Phe Ser Gln Ile Arg Tyr
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Glu Asn Lys Ile Ser Leu Glu Ser Glu Tyr Glu Lys Ile Lys Asp Ser
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Lys Phe Asp Asp Trp Lys Asn Ile Arg Gly Pro Arg Pro Trp Glu Asp
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Thr
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gaa aag aag gac cgt gta cat cat gag cct cag ctc agt gac aag gtt Glu Lys Lys Asp Arg Val His His Glu Pro Gln Leu Ser Asp Lys Val 5 10 15	150
cac aat gat att tgatagaacc aattgttgta cataaaacag atctgcgcat His Asn Asp Ile 20	202
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gat gag gca gat gaa aag act tat aat gat gca ctt ttt cga tac aat Asp Glu Ala Asp Glu Lys Thr Tyr Asn Asp Ala Leu Phe Arg Tyr Asn 40 45 50	246
ggc aca gtg gga ttg tgg gga cgg tgt atc acc ata ccc aaa aac atg Gly Thr Val Gly Leu Trp Gly Arg Cys Ile Thr Ile Pro Lys Asn Met 55 60 65	294
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Met Glu Arg Gln	105 153 201 249 297
Met Glu Arg Gln	105 153 201 249 297
Met Glu Arg Gln -35 tca agg gtt atg tca gaa aag gat gag tat cag ttt caa cat can nna Ser Arg Val Met Ser Glu Lys Asp Glu Tyr Gln Phe Gln His Xaa Xaa -30 -25 -20 gcg gng gan ctg ctt gtc ttc aat ttt ttg ctc atc ctt acc att ttg Ala Xaa Leu Leu Val Phe Asn Phe Leu Leu Thr Ile Leu -15 -10 -5 aca atc tgg tta ttt aaa aat cat cga ttc cgc ttc ttg cat gaa act Thr Ile Trp Leu Phe Lys Asn His Arg Phe Arg Phe Leu His Glu Thr 1 -5 - 10 -5 gga gga gca atg gtg tat ggc ctt ata atg gga cta att tca cga tat Gly Gly Ala Met Val Tyr Gly Leu Ile Met Gly Leu Ile Ser Arg Tyr 20 - 25 - 30 gct aca gca cca act gat att gaa agt gga act gtc tgt gac tgt gta Ala Thr Ala Pro Thr Asp Ile Glu Ser Gly Thr Val Cys Asp Cys Val aaa cta act ttc agt cca cca act ctg ctg gtt aat gtc act gac caa Lys Leu Thr Phe Ser Pro Pro Thr Leu Leu Val Asn Val Thr Asp Gln 50 - 55 gtt tat gaa tat aaa tac aaa aga gaa ata agt cag cac aac atc aat Val Tyr Glu Tyr Lys Tyr Lys Arg Glu Ile Ser Gln His Asn Ile Asn	105 153 201 249 297
Met Glu Arg Gln	105 153 201 249 297 345
The color of the	105 153 201 249 297
Met Glu Arg Gln	105 153 201 249 297 345
The color of the	105 153 201 249 297 345 393 441
Met Glu Arg Gln	105 153 201 249 297 345
Met Glu Arg Gln	105 153 201 249 297 345 393 441
Met Glu Arg Gln	105 153 201 249 297 345 393 441

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ggc tgc tat ggt gct aag act gag agc atg tgt gcc ctc gtg acg ttc Gly Cys Tyr Gly Ala Lys Thr Glu Ser Met Cys Ala Leu Val Thr Phe	208
ttc ttc atc ctc ctc ctc atc ttc att gct gag gtt gca gct gct gtg Phe Phe Ile Leu Leu Leu Ile Phe Ile Ala Glu Val Ala Ala Val 15 20 25	256
gtc gcc ctg gtg tac acc aca atg gct gag cac ttc ctg acg ttg ctg Val Ala Leu Val Tyr Thr Thr Met Ala Glu His Phe Leu Thr Leu Leu 30 35 40	304
gta gtg cct gcc atc aag aaa gat tat ggt tcc cag gaa gac ttc act Val Val Pro Ala Ile Lys Lys Asp Tyr Gly Ser Gln Glu Asp Phe Thr 45 50 55 60	352

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caa gtg tgg a Gln Val Trp A	ac acc acc sn Thr Thr 65	atg aaa ggg Met Lys Gly	ctc aag t Leu Lys C	gc cgt ggc ys Arg Gly	ttc acc 4 Phe Thr 75	₽00
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gtt aca atg a Val Thr Met L 95	aa aaa aaa				4	171
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tcc atg gct ctc atc ctc ttc tgc aac tac tat gtt tta ttt aaa ctt
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Ser Met Ala Leu Ile Leu Phe Cys Asn Tyr Tyr Val Leu Phe Lys Leu
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                                                    35
              25
ctc cgg gac aga ata gta tta ggc agg gca tac tcc tac cca ctc aac
Leu Arg Asp Arg Ile Val Leu Gly Arg Ala Tyr Ser Tyr Pro Leu Asn
                              45
          40
                                                                    705
agt tat gaa ctc aag gca aac taagctgcct ctcaacaatg agggagaact
Ser Tyr Glu Leu Lys Ala Asn
                                                                    765
cagataaaaa tattttcata cgttctattt ttttcttgtg atttttataa atatttaaga
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175

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Ser Pro Val Phe Gln Ile Pro Lys Asn Asp Asp Ile Pro Glu Gln Asp
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Ser Leu Gly Leu Ser Asn Leu Gln Lys Ser Gln Ile Gln Gly Lys Xaa
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Ala Gly Leu Gln Ser Ser Gly Lys Glu Ala Ala Leu Asn Leu Ser Phe
                                      50
                   45
Ile Ser Lys Glu Glu Met Lys Asn Thr Ser Trp Ile Arg Lys Asn Trp
                                   65
Leu Leu Val Ala Gly Ile Ser Phe Ile Gly Asp His Leu Gly Thr Tyr
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Phe Leu Gln Arg Ser Ala Lys Gln Ser Val Lys Phe Gln Ser Gln Ser
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Lys Gln Lys Ser Ile Glu Glu
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Pro Gln Ile Arg Trp Lys Ile Gln Glu Ser Ile Glu Arg Leu Arg Val
               -50
                                   -45
Ile Ala Asn Glu Ile Glu Lys Val His Arg Gly Cys Val Ile Ala Asn
           -35
                               -30
                                                   -25
Val Val Ser Gly Ser Thr Gly Ile Leu Ser Val Ile Gly Val Met Leu
                           -15
                                               -10
Ala Pro Phe Thr Ala Gly Leu Ser Leu Ser Ile Thr Ala Ala Gly Val
Gly Leu Gly Ile Ala Ser Ala Thr Ala Gly Ile Ala Ser Ser Ile Val
                15
                                   20
Glu Asn Thr Tyr Thr Arg Ser Ala Glu Leu Thr Ala Ser Arg Leu Thr
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                               35
Ala Thr Ser Thr Asp Gln Leu Glu Ala Leu Arg Asp Ile Leu His Asp
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Ile Thr Pro Asn Val Leu Ser Phe Ala Leu Asp Phe Asp Glu Ala Thr
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<210> 147 <211> 59 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -49..-1

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Gln Pro Ile Ile His Arg Trp Arg Glu Thr Asp Phe Pro Cys Ser
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Leu Arg Ser Asn
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Asp Ser Asp Phe Thr Phe Thr Leu Pro Ala Gly Gln Lys Glu Cys Phe
          15
                                  20
Tyr Gln Pro Met Pro Leu Lys Ala Ser Leu Glu Ile Glu Tyr Gln Val
             30
                              35
Leu Asp Gly Ala Gly Leu Asp Ile Asp Phe His Leu Ala Ser Pro Glu
                           50
Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr
                  65
Val Glu Thr Glu Val Gly Asp Tyr Met Phe Cys Phe Asp Asn Thr Phe
                           85
                    80
Ser Thr Ile Ser Glu Lys Val Ile Phe Phe Glu Leu Ile Pro Asp Asn
                           100
              95
Met Gly Glu Gln Ala Gln Glu Gln Glu Asp Trp Lys Lys Tyr Ile Thr
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Gly Thr Asp Ile Leu Asp Met Lys Leu Glu Asp Ile Leu Val Ser Met
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Val Phe
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Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr
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Cys Ile Arg Ser Lys Asn Gly Pro Gly Thr Ala Val His Ala Tyr Asn
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Pro Ser Thr Phe Arg Gly Gln Val
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                                 -25
Gly Trp Asp His Leu Ala Ser Phe Pro Gly Pro Ser Leu Arg Leu Phe
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                     -15
                                     -10
Ser Gly Ser Gln Ala Ser Val Cys Ser Leu Cys Ser Gly Phe Gly Ala
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Gln Glu
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Thr Val Pro Leu Leu Glu Pro Ala Asp His Ala Arg Gly Arg Ala
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His Val His Leu Pro Glu Asn Val Arg Ser Gln Ser Pro Gly His Val
                             25
Arg Arg Gly Arg Ser Gly Ala Gln Val Leu Pro Thr Gly Pro Asp Glu
                         40
                                         45
Lys Gln Val Glu Lys Ser Glu Val Asp Phe Ser Lys Ser His Ser Leu
                  55
                                 60
Val Arg Arg Phe Glu Asp Leu Lys Pro Lys Leu Ser Val Cys Lys Thr
                                    75
                70
Gly Ser Gln Val Phe Arg Ser Glu Asn Trp Lys Val Trp Ala Glu Ser
                                 90
               85
Ser Arg Gly Asp His Asp Asp Cys Leu Asp Leu Cys Ser Val Leu Cys
                             105
Trp Gly Glu Leu Leu Arg Thr Ile Pro Glu Ile Pro Pro Lys Arg Gly
                         120
                                           125
Glu Leu Lys Thr Glu Leu Leu Gly Leu Lys Glu Arg Lys His Lys Pro
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Gln Val Ser Gln Gln Glu Glu Leu Lys

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Gly Lys Asp Ile Asp Leu Asn Lys Val Arg Thr Lys Thr Ala Ala Lys
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Tyr Gly Leu Ser Ala Gln Pro Arg Leu Val Asp Ile Ile Ala Ala Val
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Pro Pro Glu
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Thr Gly His Met Gly Lys Leu Val Pro Leu Lys Glu Thr Ile Lys Gly
                            40
Phe Gln Gln Ile Leu Ala Gly Glu Tyr Asp His Leu Pro Glu Gln Ala
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Leu Ala Glu Glu His Ser Ser
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                -65
 Gln Val Leu Glu Ala Pro Gly Val Tyr Val Phe Gly Glu Leu Leu Asp
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            -50
 Met Pro Asn Val Arg Glu Leu Xaa Ala Arg Asn Leu Pro Pro Leu Thr
                            -30
        -35
 Glu Ala Gln Lys Asn Lys Leu Arg His Leu Ser Val Val Thr Leu Ala
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-15

Ala Lys Val Lys Cys Ile Pro Tyr Ala Val Leu Leu Glu Ala Leu Ala

-10

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- 5 Leu Arg Asn Val Arg Gln Leu Glu Asp Leu Val Ile Glu Ala Val Tyr · 15 20 Ala Asp Val Leu Arg Gly Ser Leu Asp Gln Arg Asn Gln Arg Leu Glu Val Asp Tyr Ser Ile Gly Arg Asp Ile Gln Arg Gln Asp Leu Ser Ala 50 Ile Ala Arg Thr Leu Gln Glu Trp Cys Val Gly Cys Glu Val Val Leu 70 Ser Gly Ile Glu Glu Gln Val Ser Arg Ala Asn Gln His Lys Glu Gln 85 Gln Leu Gly Leu Lys Gln Gln Ile Glu Ser Glu Val Ala Asn Leu Lys 100 95 Lys Thr Ile Lys Val Thr Thr Ala Ala Ala Ala Ala Ala Thr Ser Gln 115 Asp Pro Glu Gln His Leu Thr Glu Leu Arg Glu Pro Ala Pro Gly Thr 135 130 Asn Gln Arg Gln Pro Ser Lys Lys Ala Ser Lys Gly Lys Gly Leu Arg 145 150 Gly Ser Ala Lys Ile Trp Ser Lys Ser Asn 160

<210> 159 <211> 24 <212> PRT

<213> Homo sapiens

<210> 160 <211> 228 <212> PRT <213> Homo sapiens

Met Pro Thr Asn Cys Ala Ala Ala Gly Cys Ala Thr Thr Tyr Asn Lys 10 His Ile Asn Ile Ser Phe His Arg Phe Pro Leu Asp Pro Lys Arg Arg 20 25 Lys Glu Trp Val Arg Leu Val Arg Arg Lys Asn Phe Val Pro Gly Lys 35 40 His Thr Phe Leu Cys Ser Lys His Phe Glu Ala Ser Cys Phe Asp Leu 55 60 Thr Gly Gln Thr Arg Arg Leu Lys Met Asp Ala Val Pro Thr Ile Phe 75 Asp Phe Cys Thr His Ile Lys Ser Met Lys Leu Lys Ser Arg Asn Leu 90 Leu Lys Lys Asn Asn Ser Cys Ser Pro Ala Gly Pro Ser Ser Leu Lys 105 Ser Asn Ile Ser Ser Gln Gln Val Leu Leu Glu His Ser Tyr Ala Phe 120 125 Arg Asn Pro Met Glu Ala Lys Lys Arg Ile Ile Lys Leu Glu Lys Glu 135 140 Ile Ala Ser Leu Arg Arg Lys Met Lys Thr Cys Leu Gln Lys Glu Arg

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<210> 161
<211> 86
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
<400> 161
Met Asp Ley His Phe Pro

<210> 162 <211> 44 <212> PRT <213> Homo sapiens

<210> 163 <211> 314 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -58..-1 WO 99/31236 -124 - PCT/IB98/02122 ·

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<400> 163
Met Gln Asn Val Ile Asn Thr Val Lys Gly Lys Ala Leu Glu Val Ala
                     -50
        -55
Glu Tyr Leu Thr Pro Val Leu Lys Glu Ser Lys Phe Arg Glu Thr Gly
                         -35
                                        -30
Val Ile Thr Pro Glu Glu Phe Val Ala Ala Gly Asp His Leu Val His
                     -20
                                        -15
His Cys Pro Thr Trp Gln Trp Ala Thr Gly Glu Glu Leu Lys Val Lys
                 - 5
                                 1
Ala Tyr Leu Pro Thr Gly Lys Gln Phe Leu Val Thr Lys Asn Val Pro
    10
                          15
Cys Tyr Lys Arg Cys Lys Gln Met Glu Tyr Ser Asp Glu Leu Glu Ala
                                  35
    25
                         30
Ile Ile Glu Glu Asp Asp Gly Asp Gly Trp Val Asp Thr Tyr His
                     45
Asn Thr Gly Ile Thr Gly Ile Thr Glu Ala Val Lys Glu Ile Thr Leu
                  60
                                    65
Glu Asn Lys Asp Asn Ile Arg Leu Gln Asp Cys Ser Ala Leu Cys Glu
              75
                                80
Glu Glu Glu Asp Glu Asp Glu Gly Glu Ala Ala Asp Met Glu Glu Tyr
                                               100
                             95
          90
Glu Glu Ser Gly Leu Leu Glu Thr Asp Glu Ala Thr Leu Asp Thr Arg
                         110
                                           115
Lys Ile Val Glu Ala Cys Lys Ala Lys Thr Asp Ala Gly Gly Glu Asp
                      125
                                        130
Ala Ile Leu Gln Thr Arg Thr Tyr Asp Leu Tyr Ile Thr Tyr Asp Lys
                                145
                  140
Tyr Tyr Gln Thr Pro Arg Leu Trp Leu Phe Gly Tyr Asp Glu Gln Arg
              155
                                160
Gln Pro Leu Thr Val Glu His Met Tyr Glu Asp Ile Ser Gln Asp His
         170
                            175
Val Lys Lys Thr Val Thr Ile Glu Asn His Pro His Leu Pro Pro Pro
                         190
Pro Met Cys Ser Val His Pro Cys Arg His Ala Glu Val Met Lys Lys
              205
                                210
Ile Ile Glu Thr Val Ala Glu Gly Gly Glu Leu Gly Val His Met
                                   225
                 220
Tyr Leu Leu Ile Phe Leu Lys Phe Val Gln Ala Val Ile Pro Thr Ile
                                240
             235
Glu Tyr Asp Tyr Thr Arg His Phe Thr Met
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<210> 164
<211> 89
<212> PRT
<213> Homo sapiens
<221> SIGNAL
<222> -80..-1
<400> 164
Met Arg Thr Arg Thr Thr Gly Asn Pro Arg Gly Leu His Asp Thr Phe
                -75
                                       -70
Pro Arg Arg Pro Arg Leu Gly Arg Cys Ser Asp Met Asp Thr Ala Arg
                                  -55
            -60
Thr Ser Cys Ser Asp Leu Leu Pro Trp Glu Gly Val Thr Glu Pro Ala
                               -40
Leu Cys Gly Asp Gln Leu Gln Gly Thr Glu Gly Trp Leu Glu Ala Thr
```

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```
-25
                                           -20
Gln Leu Gly Arg Gly Leu Leu Ser Ala Cys Ala Pro Trp Gly Asp Gly
-15 -10 -5
Ser Thr Gln Pro Val Pro Leu Cys Ser
1 5
<210> 165
<211> 98
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -15..-1
<400> 165
Met Glu Ala Met Trp Leu Leu Cys Val Ala Leu Ala Val Leu Ala Trp
           -10
                                   <del>-</del> 5
Gly Phe Leu Trp Val Trp Asp Ser Ser Glu Arg Met Lys Ser Arg Glu
         5
                             10
Gln Gly Gly Arg Leu Gly Ala Glu Ser Arg Thr Leu Leu Val Ile Ala
    20
                      25
                                           30
His Pro Asp Asp Glu Ala Met Phe Phe Ala Pro Thr Val Leu Gly Leu
                     40
                                       45
Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys Phe Ser Ala Val Phe
                  55
Arg Arg Glu Leu Ser Glu Tyr Thr Glu Gly Leu Thr Ser Glu Pro Leu
                                75
              70
Thr Ala
<210> 166
<211> 92
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -36..-1
<400> 166
Met Leu Val Thr Gln Gly Leu Val Tyr Gln Gly Tyr Leu Ala Ala Asn
                   -30
                                     -25
Ser Arg Phe Gly Ser Leu Pro Lys Val Ala Leu Ala Gly Leu Leu Gly
                  -15
                                     -10
Phe Gly Leu Gly Lys Val Ser Tyr Ile Gly Val Cys Gln Ser Lys Phe
               1
His Phe Phe Glu Asp Gln Leu Arg Gly Ala Gly Phe Gly Pro Gln His
                                     25
                      20
    15
Asn Arg His Cys Leu Leu Thr Cys Glu Glu Cys Lys Ile Lys His Gly
                     35
Leu Ser Glu Lys Gly Asp Ser Gln Pro Ser Ala Ser
                  50
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<210> 167 <211> 351 <212> PRT

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<213> Homo sapiens <220> <221> SIGNAL <222> -16..-1 <400> 167 Met Val Pro Phe Ile Tyr Leu Gln Ala His Phe Thr Leu Cys Ser Gly -10 Trp Ser Ser Thr Tyr Arg Asp Leu Arg Lys Gly Val Tyr Val Pro Tyr 10 Thr Gln Gly Lys Trp Glu Gly Glu Leu Gly Thr Asp Leu Val Ser Ile 25 Pro His Gly Pro Asn Val Thr Val Arg Ala Asn Ile Ala Ala Ile Thr 40 45 Glu Ser Asp Lys Phe Phe Ile Asn Gly Ser Asn Trp Glu Gly Ile Leu 60 55 Gly Leu Ala Tyr Ala Glu Ile Ala Arg Pro Asp Asp Ser Pro Glu Pro 75 70 Phe Phe Asp Ser Leu Val Lys Gln Thr His Val Pro Asn Leu Phe Ser 90 Leu Gln Leu Cys Gly Ala Gly Phe Pro Leu Asn Gln Ser Glu Val Leu 110 100 105 Ala Ser Val Gly Gly Ser Met Ile Ile Gly Gly Ile Asp His Ser Leu 120 125 115 Tyr Thr Gly Ser Leu Trp Tyr Thr Pro Ile Arg Arg Glu Trp Tyr Tyr 135 140 Glu Val Ile Ile Val Arg Val Glu Ile Asn Gly Gln Asp Leu Lys Met 150 155 Asp Cys Lys Glu Tyr Asn Tyr Asp Lys Ser Ile Val Asp Ser Gly Thr 170 175 165 Thr Asn Leu Arg Leu Pro Lys Lys Val Phe Glu Ala Ala Val Lys Ser 180 185 190 Ile Lys Ala Ala Ser Ser Thr Glu Lys Phe Pro Asp Gly Phe Trp Leu 200 205 Gly Glu Gln Leu Val Cys Trp Gln Ala Gly Thr Thr Pro Trp Asn Ile 215 220 Phe Pro Val Ile Ser Leu Tyr Leu Met Gly Glu Val Thr Asn Gln Ser 235 230

Phe Arg Ile Thr Ile Leu Pro Gln Gln Tyr Leu Arg Pro Val Glu Asp

Val Ala Thr Ser Gln Asp Asp Cys Tyr Lys Phe Ala Ile Ser Gln Ser 265

Ser Thr Gly Thr Val Met Gly Ala Val Ile Met Glu Gly Phe Tyr Val

Val Phe Asp Arg Ala Arg Lys Arg Ile Gly Phe Ala Val Ser Ala Cys

His Val His Asp Glu Phe Arg Thr Ala Ala Val Glu Gly Pro Phe Cys

280

His Leu Gly His Gly Arg Leu Trp Leu Gln His Ser Thr Asp Arg

295

245

310

260

325

250

300

315

330

270

285

<210> 168 <211> 138 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -47..-1

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<400> 168
Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly Ile Asp Leu
                                           -35
                         -40
Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro Phe Val Ser
                      -25
                             -20
Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile
                -10
                          - 5.
Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu
                          10
       5
Ala Gly Leu Cys Thr Leu Gly Ser Val Ser Cys Tyr Val Ala Gly Ile
Glu Leu Leu His Gln Lys Leu Glu Leu Pro Asp Asn Val Ser Gly Glu
                     40
                                      45
Phe Gly Trp Ser Phe Cys Leu Ala Cys Val Ser Ala Pro Leu Gln Phe
                          60
                 55
Met Ala Ser Ala Leu Phe Ile Trp Ala Ala His Thr Asn Arg Arg Glu
                              75
              70
Tyr Thr Leu Met Lys Ala Tyr Arg Val Ala
          85
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<210> 169
<211> 101
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -73..-1
<400> 169

Met Asn Leu Glu Arg Val Ser Asn Glu Glu Lys Leu Asn Leu Cys Arg -65 -70 Lys Tyr Tyr Leu Gly Gly Phe Ala Phe Leu Pro Phe Leu Trp Leu Val -55 -50 Asn Ile Phe Trp Phe Tyr Arg Glu Ala Phe Leu Val Pro Ala Tyr Thr -35 Glu Gln Ser Gln Ile Lys Gly Tyr Val Trp Arg Ser Ala Val Gly Phe -20 -15 Leu Phe Trp Val Ile Val Leu Thr Ser Trp Ile Thr Ile Phe Gln Ile
-5 1 5 Tyr Arg Pro Arg Trp Gly Ala Leu Gly Asp Tyr Leu Ser Phe Thr Ile 10 15 Pro Leu Gly Thr Pro 25

<210> 170 <211> 252 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -68..-1

4400> 170
Met Pro Glu Gly Pro Glu Leu His Leu Ala Ser Gln Phe Val Asn Glu
-65 -60 -55

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Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -45 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -30 -25 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -15 -10 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly 5 Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 20 15 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 50 55 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 70 65 Arg Glu Asn Val Leu Arg Asn Leu Ala Asp Lys Ala Phe Asp Arg Pro 85 Ile Cys Glu Ala Leu Leu Asp Gln Arg Phe Phe Asn Gly Ile Gly Asn 100 Tyr Leu Arg Ala Glu Ile Leu Tyr Arg Leu Lys Ile Pro Pro Phe Glu 115 120 Lys Ala Arg Ser Val Leu Glu Ala Leu Gln Gln His Arg Pro Ser Pro 130 135 Glu Leu Thr Leu Ser Gln Lys Ile Arg Thr Lys Leu Gln Asn Ser Asp 150 145 Leu Leu Glu Leu Cys His Ser Val Pro Lys Glu Val Val Gln Leu Gly 165 160 Glu Ala Lys Asp Gly Ser Asn Leu Cys Phe Ser Lys

<210> 171
<211> 350
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -68..-1
<400> 171
Met Pro Glu Gly Pro

Met Pro Glu Gly Pro Glu Leu His Leu Ala Ser Gln Phe Val Asn Glu -65 -60 Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -45 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -30 -25 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -15 -10 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly 1 Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 55 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 70 Arg Leu Lys Ile Pro Pro Phe Glu Lys Ala Arg Ser Val Leu Glu Ala WO 99/31236 -129- PCT/IB98/02122 ·

85 80 Leu Gln Gln His Arg Pro Ser Pro Glu Leu Thr Leu Ser Gln Lys Ile 105 · 100 Arg Thr Lys Leu Gln Asn Pro Asp Leu Leu Glu Leu Cys His Ser Val 120 115 Pro Lys Glu Val Asp Gln Leu Gly Gly Arg Gly Tyr Gly Ser Glu Ser 130 135 Gly Glu Glu Asp Phe Ala Ala Phe Arg Ala Trp Leu Arg Cys Tyr Gly 150 145 Met Pro Gly Met Ser Ser Leu Gln Asp Arg His Gly Arg Thr Ile Trp 165 160 Phe Gln Gly Asp Pro Gly Pro Leu Ala Pro Lys Gly Arg Lys Ser Arg 185 180 175 Lys Lys Lys Ser Lys Ala Thr Gln Leu Ser Pro Glu Asp Arg Val Glu 195 200 Asp Ala Leu Pro Pro Ser Lys Ala Pro Ser Lys Thr Arg Arg Ala Lys 215 210 Arg Asp Leu Pro Lys Arg Thr Ala Thr Gln Arg Pro Glu Gly Thr Ser 230 225 Leu Gln Gln Asp Pro Glu Ala Pro Thr Val Pro Lys Lys Gly Arg Arg 245 250 240 Lys Gly Arg Gln Ala Ala Ser Gly His Cys Arg Pro Arg Lys Val Lys 265 260 255 Ala Asp Ile Pro Ser Leu Glu Pro Glu Gly Thr Ser Ala Ser 275

<210> 172 <211> 390 <212> PRT <213> Homo sapiens <220>

<221> SIGNAL <222> -68..-1

<400> 172 Met Pro Glu Gly Pro Glu Leu His Leu Ala Ser Gln Phe Val Asn Glu -60 -65 Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -45 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -25 -30 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -15 -10 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly 5 1 Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 40 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 55 50 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 70 65 Arg Glu Asn Val Leu Arg Asn Leu Ala Asp Lys Ala Phe Asp Arg Pro 90 85 Ile Cys Glu Ala Leu Leu Asp Gln Arg Phe Phe Asn Gly Ile Gly Asn 100 105 Tyr Leu Arg Ala Glu Ile Leu Tyr Arg Leu Lys Ile Pro Pro Phe Glu 115

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Lys Ala Arg Ser Val Leu Glu Ala Leu Gln Gln His Arg Pro Ser Pro 130 135 Glu Leu Thr Leu Ser Gln Lys Ile Arg Thr Lys Leu Gln Asn Pro Asp 150 145 Leu Leu Glu Leu Cys His Ser Val Pro Lys Glu Val Val Gln Leu Gly 165 Gly Arg Gly Tyr Gly Ser Glu Ser Gly Glu Glu Asp Phe Ala Ala Phe 175 180 Arg Ala Trp Leu Arg Cys Tyr Gly Met Pro Gly Met Ser Ser Leu Gln 195 Asp Arg His Gly Arg Thr Ile Trp Phe Gln Gly Asp Pro Gly Pro Leu 215 210 Ala Pro Lys Gly Arg Lys Ser Arg Lys Lys Lys Ser Lys Ala Thr Gln 225 230 Leu Ser Pro Glu Asp Arg Val Glu Asp Ala Leu Pro Pro Ser Lys Ala 245 240 Pro Ser Arg Thr Arg Arg Ala Lys Arg Asp Leu Pro Lys Arg Thr Ala 260 265 255 Thr Gln Arg Pro Glu Gly Thr Ser Leu Gln Gln Asp Pro Glu Ala Pro 275 280 Thr Val Pro Lys Lys Gly Arg Arg Lys Gly Arg Gln Ala Ala Ser Gly 290 295 His Cys Arg Pro Arg Lys Val Lys Ala Asp Ile Pro Ser Leu Glu Pro 305 310 Glu Gly Thr Ser Ala Ser 320

<211> 190 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -82..-1 <400> 173 Met Tyr Val Trp Pro Cys Ala Val Val Leu Ala Gln Tyr Leu Trp Phe -75 -70 His Arg Arg Ser Leu Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala Gly -55 -65 -60 Val Ser Leu Pro Gly Ile Leu Thr Ala Lys Cys Gly Ala Glu Val Ile -40 -45 Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg Gln -20 -25 -30 Ser Cys Gln Met Asn Asn Leu Pro His Leu Gln Val Val Gly Leu Thr -10 -5 Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp Ile 5 10 Ile Leu Ala Ser Asp Val Phe Phe Glu Pro Glu Asp Phe Glu Asp Ile 20 25 Leu Ala Thr Ile Tyr Phe Leu Met His Lys Asn Pro Lys Val Gln Leu 40 35 Trp Ser Thr Tyr Gln Val Arg Ser Ala Asp Trp Ser Leu Glu Ala Leu 55 50 Leu Tyr Lys Trp Asp Met Lys Cys Val His Ile Pro Leu Glu Ser Phe 70 Asp Ala Asp Lys Glu Asp Ile Ala Glu Ser Thr Leu Pro Gly Arg His

80 85 90
Thr Val Glu Met Leu Val Ile Ser Phe Ala Lys Asp Ser Leu

<210> 173

100 105 95

<210> 174 <211> 285 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -232..-1 <400> 174 Met Gly Cys Val Phe Gln Ser Thr Glu Asp Lys Arg Ile Phe Lys Ile -230 -225 -220 Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr Val Leu -215 -210 -205 Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg **-1**95 **-1**90 **-18**5 -200 Val His Leu Met Gly Asp Asn Leu Cys Asn Asp Gly Ser Leu Leu Leu -180 -175 -170 Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg -160 -155 -165 Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val -140 -145 -150 Leu Pro Glu Glu Pro Lys Glu Leu Met Val His Val Gly Gly Leu Ile -125 -130 Gln Met Gly Cys Val Phe Gln Ser Thr Glu Val Lys His Val Thr Lys -115 -110 -105 Val Glu Trp Ile Phe Ser Gly Arg Arg Ala Lys Glu Glu Ile Val Phe -95 -100 Arg Tyr Tyr His Lys Leu Arg Met Ser Ala Glu Tyr Ser Gln Ser Trp -85 -80 -75 Gly His Phe Gln Asn Arg Val Asn Leu Val Gly Asp Ile Phe Arg Asn -65 Asp Gly Ser Ile Met Leu Gln Gly Val Arg Glu Ser Asp Gly Gly Asn -55 -50 -45 Tyr Thr Cys Ser Ile His Leu Gly Asn Leu Val Phe Lys Lys Thr Ile -35 -30 Val Leu His Val Ser Pro Glu Glu Pro Arg Thr Leu Val Thr Pro Ala -15 -20 Ala Leu Arg Pro Leu Val Leu Gly Gly Asn Gln Leu Val Ile Ile Val 1 5 **-**5 Gly Ile Val Cys Ala Thr Ile Leu Leu Pro Val Leu Ile Leu Ile 15 20 Val Lys Lys Thr Cys Gly Asn Lys Ser Ser Val Asn Ser Thr Val Leu 35 30 Val Lys Asn Thr Lys Lys Thr Asn Pro Lys Lys Lys 50 45

<210> 175 <211> 153 <212> PRT

<213> Homo sapiens

<400> 175 Met Gly Cys Val Phe Gln Ser Thr Val Asp Lys Cys Ile Phe Lys Ile 10 5 Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr Val Leu WO 99/31236 -132- PCT/IB98/02122-

25 20 Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg 3.5 40 Val His Leu Met Gly Asp Ile Leu Cys Asn Asp Gly Ser Leu Leu 55 60 Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg 75 70 Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val 90 85 Leu Pro Glu Glu Pro Lys Glu Leu Met Val His Val Gly Gly Leu Ile 105 100 Gln Met Gly Cys Val Phe Gln Ser Thr Glu Val Lys His Val Thr Lys 120 115 Val Glu Trp Ile Phe Ser Gly Arg Arg Ala Lys Val Thr Arg Arg Lys 135 His His Cys Val Arg Glu Gly Ser Gly 150

<210> 176 <211> 49 <212> PRT <213> Homo sapiens

<210> 177
<211> 99
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -24..-1

<400> 177 Met Lys Ser Ala Lys Leu Gly Phe Leu Leu Arg Phe Phe Ile Phe Cys -20 -15 Ser Leu Asn Thr Leu Leu Leu Gly Gly Val Asn Lys Ile Ala Glu Lys - 5 Ile Cys Gly Asp Leu Lys Asp Pro Cys Lys Leu Asp Met Asn Phe Gly 15 2.0 Ser Cys Tyr Glu Val His Phe Arg Tyr Phe Tyr Asn Arg Thr Ser Lys 30 35 Arg Cys Glu Thr Phe Val Phe Ser Gly Cys Asn Gly Asn Leu Asn Asn 50 45 Phe Lys Leu Lys Ile Glu Arg Glu Val Ala Cys Val Ala Lys Tyr Lys Pro Pro Arg 75

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<211> 95
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 178
Met Ala Ser Pro Ala Val Asn Arg Trp Lys Arg Pro Arg Leu Lys Pro
                           -30
                                              -25
Val Trp Pro Arg Arg Leu Glu Ser Trp Leu Leu Leu Asp Ala Leu Leu
  -20
                       -15
                                    -10
Arg Leu Gly Asp Thr Lys Lys Lys Arg Gln Pro Glu Ala Ala Thr Lys
                  1
                                  5
Ser Cys Val Arg Ser Ser Cys Gly Gly Pro Ser Gly Asp Gly Pro Pro
                              20
          15
Pro Cys Leu Gln Gln Pro Asp Pro Arg Ala Leu Ser Gln Ala Phe Ser
     30
                          35
                                              40
Arg Ser Phe Pro Leu Phe Pro Ser Leu Ala Gly Lys Ser Met Ile
   45
                       50
<210> 179
<211> 121
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 179
Met Met Leu Pro Gln Trp Leu Leu Leu Phe Leu Leu Phe Phe Phe
        -20
                              -15
Leu Phe Leu Leu Thr Arg Gly Ser Leu Ser Pro Thr Lys Tyr Asn Leu
Leu Glu Leu Lys Glu Ser Cys Ile Arg Asn Gln Asp Cys Glu Thr Gly
10
                   15
                                       20
Cys Cys Gln Arg Ala Pro Asp Asn Cys Glu Ser His Cys Ala Glu Lys
                                  35
               30
Gly Ser Glu Gly Ser Leu Cys Gln Thr Gln Val Phe Phe Gly Gln Tyr
                              50
           45
Arg Ala Cys Pro Cys Leu Arg Asn Leu Thr Cys Ile Tyr Ser Lys Asn
     . 60
                           65
Glu Lys Trp Leu Ser Ile Ala Tyr Gly Arg Cys Gln Lys Ile Gly Arg
                       80
                                          85
Gln Lys Leu Ala Lys Lys Met Phe Phe
                   95
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<210> 180

<210> 178

<211> 59

<212> PRT

<213> Homo sapiens

<400> 180

Met Ile Leu Cys Phe Leu Leu Pro His His Arg Leu Gln Glu Ala Arg

10 15
Gln Ile Gln Val Leu Lys Met Leu Pro Arg Glu Lys Leu Arg Arg Arg
20 25 30
Glu Glu Arg Lys Gln Ile Asn Gly Lys Lys Glu Arg Thr Lys Tyr Glu
35
Thr Pro Arg Lys Arg Glu Gly Lys Lys Lys Lys
50 55

<210> 181 <211> 86 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -14..-1 <400> 181 Met Val Ala Leu Asn Leu Ile Leu Val Pro Cys Cys Ala Ala Trp Cys -10 -5 Asp Pro Arg Arg Ile His Ser Gln Asp Asp Val Pro Arg Ser Ser Ala 10 Ala Asp Thr Gly Ser Ala Met Gln Arg Arg Glu Ala Trp Ala Gly Trp 25 Arg Arg Ser Gln Pro Phe Ser Val Gly Leu Pro Ser Ala Glu Arg Leu 40 45 Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg Ser Leu Val Gly Glu Gly 55 .. . 60 Tyr Arg Ile Cys Asp Leu 70

<210> 182 <211> 165 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -58..-1 <400> 182

Met Thr Arg Leu Cys Leu Pro Arg Pro Glu Ala Arg Glu Asp Pro Ile -50 -55 Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser Pro -35 -30 Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu Leu -15 -20 Asp Ser Val Leu Trp Leu Gly Ala Leu Gly Leu Thr Ile Gln Ala Val - 5 1 Phe Ser Thr Thr Gly Pro Ala Leu Leu Leu Leu Val Ser Phe Leu 20 15 Thr Phe Asp Leu Leu His Arg Pro Ala Gly His Thr Leu Pro Gln Arg 30 Lys Leu Leu Thr Arg Gly Gln Ser Gln Gly Ala Gly Glu Gly Pro Gly 50 45 Gln Gln Glu Ala Leu Leu Gln Met Gly Thr Val Ser Gly Gln Leu 60 65 Ser Leu Gln Asp Ala Leu Leu Leu Leu Leu Met Gly Leu Gly Pro Leu

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80
               75
 Leu Arg Ala Cys Gly Met Pro Leu Thr Leu Leu Gly Leu Ala Phe Cys
                   95
      90
 Leu His Pro Trp Ala
       105
 <210> 183
 <211> 80
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -35..-1
 <400> 183
 Met Pro Phe Gln Phe Gly Thr Gln Pro Arg Arg Phe Pro Val Glu Gly
           -30
                                  -25
Gly Asp Ser Ser Ile Glu Leu Glu Pro Gly Leu Ser Ser Ser Ala Ala
                                       -5
                       -10
              -15
 Cys Asn Gly Lys Glu Met Ser Pro Thr Arg Gln Leu Arg Arg Cys Pro
                 5
                                    10
 Gly Ser His Cys Leu Thr Ile Thr Asp Val Pro Val Thr Val Tyr Ala
                                . 25
            20
 Thr Thr Arg Lys Pro Pro Ala Gln Ser Ser Lys Glu Met His Pro Lys
            35
                          40
 <210> 184
 <211> 73
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -21..-1
  <400> 184
 Met Ala Pro Gln Thr Leu Leu Pro Val Leu Val Leu Cys Val Leu Leu
                   -15 -10
  Leu Gln Ala Gln Gly Gly Tyr Arg Asp Lys Met Arg Met Gln Arg Ile
                                5
                  1
  Lys Val Cys Glu Lys Arg Pro Ser Ile Asp Leu Cys Ile His His Cys
                  20
  Ser Cys Phe Gln Lys Cys Glu Thr Asn Lys Ile Cys Cys Ser Ala Phe
                                     40
                   35
  Cys Gly Asn Ile Cys Met Ser Ile Leu
     45
                      50
  <210> 185
  <211> 98
  <212> PRT
  <213> Homo sapiens
  Met Leu Gly Ala Glu Thr Glu Glu Lys Leu Phe Asp Ala Pro Leu Ser
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<210> 186 <211> 112 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1

<210> 187 <211> 70 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -44..-1

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<210> 188
<211> 92
<212> PRT
<213> Homo sapiens
<221> SIGNAL
<222> -13..-1
<400> 188
Met Leu Phe Ser Leu Ser Leu Leu Ser Asn Leu Asn Gln Ile Gly Ser
                              -5
         -10
Ser His Leu Asp Arg Pro His Ile Pro Gly Gln Ser Ala Gln Leu Phe
                                        15
                       10
Ile Tyr Gln Met Ser Ser Gln Gln Leu Gln Gln Gln Pro Ser Ala Asn
                        30
                   25
Lys Lys Ala Gly Lys Ile His Asn Thr Pro Phe Ala Asn Gln Leu Asn
                                 45
               40
Pro Thr Gln His Leu Ala Lys Pro Phe Gln Gln Ile Leu Pro Gly Arg
                              60
          55
Gln Ser Gly Ser Leu Thr Ser Pro Phe Leu Ala Cys
                           75
<210> 189
<211> 207
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -42..-1
Met His Ile Leu Gln Leu Leu Thr Thr Val Asp Asp Gly Ile Gln Ala
                           -35
                                            -30
     -40
Ile Val His Cys Pro Asp Thr Gly Lys Asp Ile Trp Asn Leu Leu Phe
                                         -15
                       -20
Asp Leu Val Cys His Glu Phe Cys Gln Ser Asp Asp Pro Pro Ile Ile
                                   1
                   -5
Leu Gln Glu Gln Lys Thr Val Leu Ala Ser Val Phe Ser Val Leu Ser
                       15
Ala Ile Tyr Ala Ser Gln Thr Glu Gln Glu Tyr Leu Lys Ile Glu Lys
                       30
       25
Val Asp Leu Pro Leu Ile Asp Ser Leu Ile Arg Val Leu Gln Asn Met
                                          50
                       4.5
```

Glu Gln Cys Gln Lys Lys Pro Glu Asn Ser Ala Glu Ser Asn Thr Glu 65 60 Glu Thr Lys Arg Thr Asp Leu Thr Gln Asp Asp Leu His Leu Lys Ile 80 Leu Lys Asp Ile Leu Cys Glu Phe Leu Ser Asn Ile Phe Gln Ala Leu 95 90 Thr Lys Glu Thr Val Ala Gln Gly Val Lys Glu Gly Gln Leu Ser Lys 110 Gln Lys Cys Ser Ser Ala Phe Gln Asn Leu Leu Pro Phe Tyr Ser Pro 125 130 120 Val Val Glu Asp Phe Ile Lys Ile Leu Arg Glu Val Asp Lys Ala Leu 140 145 Ala Asp Asp Leu Glu Lys Asn Phe Pro Ser Leu Lys Val Gln Thr

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155 160 165

<210> 190 <211> 201 <212> PRT <213> Homo sapiens <400> 190 Met Gln Val Ala Leu Lys Glu Asp Leu Asp Ala Leu Lys Glu Lys Phe 10 Arg Thr Met Glu Ser Asn Gln Lys Ser Ser Phe Gln Glu Ile Pro Lys 20 25 Leu Asn Glu Glu Leu Leu Ser Lys Gln Lys Gln Leu Glu Lys Ile Glu 40 Ser Gly Glu Met Gly Leu Asn Lys Val Trp Ile Asn Ile Thr Glu Met 55 60 Asn Lys Gln Ile Ser Leu Leu Thr Ser Ala Val Asn His Leu Lys Ala 70 75 Asn Val Lys Ser Ala Ala Asp Leu Ile Ser Leu Pro Thr Thr Val Glu 90 8.5 Gly Leu Gln Lys Ser Val Ala Ser Ile Gly Asn Thr Leu Asn Ser Val 100 105 110 His Leu Ala Val Glu Ala Leu Gln Lys Thr Val Asp Glu His Lys Lys 120 125 Thr Met Glu Leu Leu Gln Ser Asp Met Asn Gln His Phe Leu Lys Glu 135 140 Thr Pro Gly Ser Asn Gln Ile Ile Pro Ser Pro Ser Ala Thr Ser Glu 150 155 Leu Asp Asn Lys Thr His Ser Glu Asn Leu Lys Gln Met Gly Asp Arg 170 165 Ser Ala Thr Leu Lys Arg Gln Ser Leu Asp Gln Val Thr Asn Arg Thr Asp Thr Val Lys Ile Gln Lys Lys 195

<210> 191 <211> 379 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<400> 191

<222> -37..-1

 Met
 Pro
 His
 Ser
 Leu
 His
 Pro
 Ser
 Ile
 Pro
 Cys
 Pro
 Arg
 Gly
 His

 Gly
 Ala
 Glu
 Ala
 Leu
 Val
 Leu
 Leu
 Ser
 Ala
 Cys
 Leu
 Val
 Thr

 Leu
 Trp
 Gly
 Leu
 Gly
 Pro
 Pro
 Glu
 His
 Thr
 Leu
 Arg
 Tyr
 Leu
 Val
 Cys

 Leu
 His
 Leu
 Gly
 Leu
 Leu
 Leu
 Arg
 Tyr
 Leu
 Val
 Cys

 Leu
 Ala
 Glu
 Leu
 Arg
 His
 Ile
 His
 Thr
 Leu
 Arg
 Gly
 Val
 Cys
 Leu
 Leu
 Arg
 Gly
 Ser
 Leu
 Arg
 Gly
 Ser
 Arg
 Tyr
 Arg
 Gly
 Ser
 Leu
 Arg
 Gly
 Ser
 Leu
 Arg
 Gly
 Ser

70 65 60 Val Gly Pro Pro Phe Thr Trp Met Leu Ala Leu Leu Gly Leu Ser Gln 85 Ala Leu Asn Ile Leu Leu Gly Leu Lys Gly Leu Ala Pro Ala Glu Ile 100 Ser Ala Val Cys Glu Lys Gly Asn Phe Asn Val Ala His Gly Leu Ala 115 120 Trp Ser Tyr Tyr Ile Gly Tyr Leu Arg Leu Ile Leu Pro Glu Leu Gln 135 130 Ala Arg Ile Arg Thr Tyr Asn Gln His Tyr Asn Asn Leu Leu Arg Gly 150 145 Ala Val Ser Gln Arg Leu Tyr Ile Leu Leu Pro Leu Asp Cys Gly Val 165 Pro Asp Asn Leu Ser Met Ala Asp Pro Asn Ile Arg Phe Leu Asp Lys 180 Leu Pro Gln Gln Thr Gly Asp Arg Ala Gly Ile Lys Asp Arg Val Tyr 200 195 Ser Asn Ser Ile Tyr Glu Leu Leu Glu Asn Gly Gln Arg Ala Gly Thr 215 210 Cys Val Leu Glu Tyr Ala Thr Pro Leu Gln Thr Leu Phe Ala Met Ser 225 230 Gln Tyr Ser Gln Ala Gly Phe Ser Arg Glu Asp Arg Leu Glu Gln Ala 245 Lys Leu Phe Cys Arg Thr Leu Glu Asp Ile Leu Ala Asp Ala Pro Glu 260 255 Ser Gln Asn Asn Cys Arg Leu Ile Ala Tyr Gln Glu Pro Ala Asp Asp 280 275 Ser Ser Phe Ser Leu Ser Gln Glu Val Leu Arg His Leu Arg Gln Glu 290 Glu Lys Glu Glu Val Thr Val Gly Ser Leu Lys Thr Ser Ala Val Pro 310 305 Ser Thr Ser Thr Met Ser Gln Glu Pro Glu Leu Leu Ser Gly Met 320 325 Gly Lys Pro Leu Pro Leu Arg Thr Asp Phe Ser 335

<210> 192 <211> 112 <212> PRT <213> Homo sapiens

<400> 192 Met Pro Ser Glu Gly Arg Cys Trp Glu Thr Leu Lys Ala Leu Arg Ser 10 Ser Asp Lys Gly Arg Leu Cys Tyr Tyr Arg Asp Trp Leu Leu Arg Arg 25 Glu Asp Val Leu Glu Glu Cys Met Ser Leu Pro Lys Leu Ser Ser Tyr 40 Ser Gly Trp Val Val Glu His Val Leu Pro His Met Gln Glu Asn Gln 55 60 Pro Leu Ser Glu Thr Ser Pro Ser Ser Thr Ser Ala Ser Ala Leu Asp 75 70 Gln Pro Ser Phe Val Pro Lys Ser Pro Asp Ala Ser Ser Ala Phe Ser 90 85 Pro Ala Ser Pro Ala Thr Pro Asn Gly Thr Lys Gly Lys Lys Lys

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<211> 43
<212> PRT
<213> Homo sapiens
<400> 193
Ser Leu Pro Gln Ala Leu Trp Phe Gln Phe Phe Tyr His Ser Gly Ser
                                   10
Ser Leu Glu Ser Pro Gly Met Leu Asn Gly Pro Phe Gln His Arg Asn
           20
                           25
Ser Arg Ile Met Thr His Arg Ser Ala Glu Lys
       35
                          40
<210> 194
<211> 51
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 194
Met Leu Arg Ile Ala Leu Thr Leu Ile Pro Ser Met Leu Ser Arg Ala
                    -10
                                          -5
Ala Gly Trp Cys Trp Tyr Lys Glu Pro Thr Gln Gln Phe Ser Tyr Leu
                                  10
Cys Leu Pro Cys Leu Ser Trp Asn Lys Lys Gly Asn Val Leu Gln Leu
                        25
   20
Pro Asn Phe
      35
<210> 195
<211> 244
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -18..-1
<400> 195
Met Ala Asn Pro Lys Leu Leu Gly Leu Glu Leu Ser Glu Ala Glu Ala
                                                  - 5
           -15
                               -10
Ile Gly Ala Asp Ser Ala Arg Phe Glu Glu Leu Leu Gln Ala Ser
                                          10
Lys Glu Leu Gln Gln Ala Gln Thr Thr Arg Pro Glu Ser Thr Gln Ile
                  20
Gln Pro Gln Pro Gly Phe Cys Ile Lys Thr Asn Ser Ser Glu Gly Lys
                                   40
Val Phe Ile Asn Ile Cys His Ser Pro Ser Ile Pro Pro Pro Ala Asp
                               55
Val Thr Glu Glu Glu Leu Leu Gln Met Leu Glu Glu Asp Gln Ala Gly
                           70
Phe Arg Ile Pro Met Ser Leu Gly Glu Pro His Ala Glu Leu Asp Ala
                                           90
                      85
Lys Gly Gln Gly Cys Thr Ala Tyr Asp Val Ala Val Asn Ser Asp Phe
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100

105

Tyr Arg Arg Met Gln Asn Ser Asp Phe Leu Arg Glu Leu Val Ile Thr

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125
            115
                            120
Ile Ala Arg Glu Gly Leu Glu Asp Ile Tyr Asn Leu Gln Leu Asn Pro
    130 135 140
Glu Trp Arg Met Met Lys Asn Arg Pro Phe Met Gly Ser Ile Ser Gln
   145 150
                                      155
Gln Asn Ile Arg Ser Glu Gln Arg Pro Arg Ile Gln Glu Leu Gly Asp
                   165
                                   170
Leu Tyr Thr Pro Ala Pro Gly Arg Ala Glu Ser Gly Pro Glu Lys Pro
175
               180
                         185
His Leu Asn Leu Trp Leu Glu Ala Pro Asp Leu Leu Leu Ala Glu Val
                200 205
            195
Asp Leu Pro Lys Leu Asp Gly Ala Leu Gly Leu Ser Leu Glu Ile Gly
                215
         210
Arg Thr Ala Trp
      225
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<210> 196 <211> 353 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -34..-1

<400> 196 Met Glu Arg Gly Leu Lys Ser Ala Asp Pro Arg Asp Gly Thr Gly Tyr -25 -20 -30 Thr Gly Trp Ala Gly Ile Ala Val Leu Tyr Leu His Leu Tyr Asp Val -10 -15 Phe Gly Asp Pro Ala Tyr Leu Gln Leu Ala His Gly Tyr Val Lys Gln 10 Ser Leu Asn Cys Leu Thr Lys Arg Ser Ile Thr Phe Leu Cys Gly Asp 25 20 Ala Gly Pro Leu Ala Val Ala Val Leu Tyr His Lys Met Asn Asn 40 Glu Lys Gln Ala Glu Asp Cys Ile Thr Arg Leu Ile His Leu Asn Lys 50 55 Ile Asp Pro His Ala Pro Asn Glu Met Leu Tyr Gly Arg Ile Gly Tyr 70 75 Ile Tyr Ala Leu Leu Phe Val Asn Lys Asn Phe Gly Val Glu Lys Thr 85 Pro Gln Ser His Ile Gln Gln Ile Cys Glu Thr Ile Leu Thr Ser Gly 100 105 Glu Asn Leu Ala Arg Lys Arg Asn Phe Thr Ala Lys Ser Pro Leu Met 120 Tyr Glu Trp Tyr Gln Glu Tyr Tyr Val Gly Ala Ala His Gly Leu Ala 130 135 140 Gly Ile Tyr Tyr Leu Met Gln Pro Ser Leu Gln Val Ser Gln Gly 150 155 145 Lys Leu His Ser Leu Val Lys Pro Ser Val Asp Tyr Val Cys Gln Leu 165 170 Lys Phe Pro Ser Gly Asn Tyr Pro Pro Cys Ile Gly Asp Asn Arg Asp 185 Leu Leu Val His Trp Cys His Gly Ala Pro Gly Val Ile Tyr Met Leu 195 200 Ile Gln Ala Tyr Lys Val Phe Arg Glu Glu Lys Tyr Leu Cys Asp Ala 220 215 210 Tyr Gln Cys Ala Asp Val Ile Trp Gln Tyr Gly Leu Leu Lys Lys Gly WO 99/31236 -142- PCT/IB98/02122 -

Tyr Gly Leu Cys His Gly Ser Ala Gly Asn Ala Tyr Ala Phe Leu Thr 245 250 Leu Tyr Asn Leu Thr Gln Asp Met Lys Tyr Leu Tyr Arg Ala Cys. Lys 265 260 Phe Ala Glu Trp Cys Leu Glu Tyr Gly Glu His Gly Cys Arg Thr Pro 280 275 Asp Thr Pro Phe Ser Leu Phe Glu Gly Met Ala Gly Thr Ile Tyr Phe 290 295 Leu Ala Asp Leu Leu Val Pro Thr Lys Ala Arg Phe Pro Ala Phe Glu 310 315 Leu

<210> 197 <211> 30 <212> PRT <213> Homo sapiens

<210> 198 <211> 112 <212> PRT <213> Homo sapiens <220>

<221> SIGNAL <222> -48..-1

<400> 198 Met Gln Asp Thr Gly Ser Val Val Pro Leu His Trp Phe Gly Phe Gly -40 -35 Tyr Ala Ala Leu Val Ala Ser Gly Gly Ile Ile Gly Tyr Val Lys Ala -25 -30 Gly Ser Val Pro Ser Leu Ala Ala Gly Leu Leu Phe Gly Ser Leu Ala -5 -10 Gly Leu Gly Ala Tyr Gln Leu Ser Gln Asp Pro Arg Asn Val Trp Val 10 Phe Leu Ala Thr Ser Gly Thr Leu Ala Gly Ile Met Gly Met Arg Phe 20 Tyr His Ser Gly Lys Phe Met Pro Ala Gly Leu Ile Ala Gly Ala Ser 40 Leu Leu Met Val Ala Lys Val Gly Val Ser Met Phe Asn Arg Pro His 55

<210> 199
<211> 54
<212> PRT
<213> Homo sapiens
<400> 199
Glu Ile Ala Gly Tyr Gly Ala Glu Gly Phe Ser Ser Val Leu Gly Tyr

Pro Arg Trp His Arg Leu Pro Pro Gln Ser Leu Gln His His Gln Tyr
20 25 30

Cys Gln Arg Arg Trp Pro Asp Arg Arg Cys Leu Gln Ser His Thr Gln
35 40 45

Ser Ser Gly His Leu Pro
50

<211> 151 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 <400> 200 Met Ala Ala Ser Thr Ser Met Xaa Pro Val Ala Val Thr Ala Ala Val -15 Ala Pro Val Leu Ser Ile Asn Ser Asp Phe Ser Asp Leu Arg Glu Ile 1 Lys Lys Gln Leu Leu Ile Ala Gly Leu Thr Arg Glu Arg Gly Leu 20 Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser Leu Pro Ala 35 Leu Pro Xaa Gly Gln Leu Gln Pro Pro Pro Pro Ile Thr Glu Glu Asp . .55 50 Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr Phe Asp Val 65 Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys Asn Ser Lys 85 Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val Arg Ala Ile 105 100 Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe Arg Thr Asn 115 110

130

<210> 201 <211> 228 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -25..-1

125

Gly Lys Val Lys Ser Phe Lys

<210> 200

 Met Ser Met Ala Val Glu Thr Phe Gly Phe Phe Met Ala Thr Val Gly -25
 -20
 -15
 -10

 Leu Leu Met Leu Gly Val Thr Leu Pro Asn Ser Tyr Trp Arg Val Ser -5
 1
 5

 Thr Val His Gly Asn Val Ile Thr Thr Asn Thr Ile Phe Glu Asn Leu 10
 15
 20

 Trp Phe Ser Cys Ala Thr Asp Ser Leu Gly Val Tyr Asn Cys Trp Glu 25
 30
 35

 Phe Pro Ser Met Leu Ala Leu Ser Gly Tyr Ile Gln Ala Cys Arg Ala 40
 45
 50

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Leu Met Ile Thr Ala Ile Leu Leu Gly Phe Leu Gly Leu Leu Gly Ile Ala Gly Leu Arg Cys Thr Asn Ile Gly Gly Leu Glu Leu Ser Arg 80 Lys Ala Lys Leu Ala Ala Thr Ala Gly Ala Pro His Ile Leu Ala Gly 100 95 Ile Cys Gly Met Val Ala Ile Ser Trp Tyr Ala Phe Asn Ile Thr Arg 115 105 110 Asp Phe Phe Asp Pro Leu Tyr Pro Gly Thr Lys Tyr Glu Leu Gly Pro 130 125 120 Ala Leu Tyr Leu Gly Trp Ser Ala Ser Leu Ile Ser Ile Leu Gly Gly 150 145 140 Leu Cys Leu Cys Ser Ala Cys Cys Cys Gly Ser Asp Glu Asp Pro Ala 165 155 160 Ala Ser Ala Arg Arg Pro Tyr Gln Ala Pro Val Ser Val Met Pro Val 175 180 170 Ala Thr Ser Asp Gln Glu Gly Asp Ser Ser Phe Gly Lys Tyr Gly Arg 190 Asn Ala Tyr Val 200

<210> 202 <211> 64 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -47..-1

<210> 203 <211> 146 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -31..-1

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<210> 204 <211> 87 <212> PRT <213> Homo sapiens

<210> 205
<211> 40
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -27..-1

85

<210> 206 <211> 154 <212> PRT <213> Homo sapiens

<400> 206 Met Gly Ser Leu Ser Gly Leu Arg Leu Ala Ala Gly Ser Cys Phe Arg

10 Leu Cys Glu Arg Asp Val Ser Ser Ser Leu Arg Leu Thr Arg Ser Ser 30 . 25 20 Asp Leu Lys Arg Ile Asn Gly Phe Cys Thr Lys Pro Gln Glu Ser Pro 40 Gly Ala Pro Ser Arg Thr Tyr Asn Arg Val Pro Leu His Lys Pro Thr 55 Asp Trp Gln Lys Lys Ile Leu Ile Trp Ser Gly Arg Phe Lys Lys Glu 75 70 Asp Glu Ile Pro Glu Thr Val Ser Leu Glu Met Leu Asp Ala Ala Lys 90 Asn Lys Met Arg Val Lys Ser Ser Tyr Leu Met Ile Ala Leu Thr Val 105 100 Val Gly Cys Ile Phe Met Val Ile Glu Gly Lys Lys Ala Ala Gln Arg 115 120 125 His Glu Thr Leu Thr Ser Leu Asn Leu Glu Lys Lys Ala Arg Leu Lys 135 Glu Glu Ala Ala Met Lys Ala Lys Thr Glu 150

<210> 207 <211> 101 <212> PRT <213> Homo sapiens

<400> 207 Met Val Cys Glu Lys Cys Glu Lys Lys Leu Gly Thr Val Ile Thr Pro 10 Asp Thr Trp Lys Asp Gly Ala Arg Asn Thr Thr Glu Ser Gly Gly Arg 25 20 Lys Leu Asn Lys Asn Lys Ala Leu Thr Ser Lys Lys Ala Arg Phe Asp 40 Pro Tyr Gly Lys Asn Lys Phe Ser Thr Cys Arg Ile Cys Lys Ser Ser 55 Val His Gln Pro Gly Ser His Tyr Cys Gln Gly Cys Ala Tyr Lys Lys 75 70 Gly Ile Cys Ala Met Cys Gly Lys Lys Val Leu Asp Thr Lys Asn Tyr 90 85 Lys Gln Thr Ser Val

<210> 208
<211> 456
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -22..-1

100

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30
Glu Glu Glu Glu Glu Arg Lys Lys Cys Pro Lys Lys Ala Ser
                                 55
                         50
Phe Ala Ser Ala Ser Ala Glu Val Gly Lys Lys Gly Lys Lys Cys
                     65
Gln Lys Gln Gly Pro Pro Cys Ser Asp Ser Glu Glu Glu Val Glu Arg
                  80
Lys Lys Cys His Lys Gln Ala Leu Val Gly Ser Asp Ser Ala Glu
                                100
Asp Glu Lys Arg Lys Arg Lys Cys Gln Lys His Ala Pro Ile Asn Ser
                                               120
                            115
Ala Gln His Leu Asp Asn Val Asp Gln Thr Gly Pro Lys Ala Trp Lys
                                         135
               130
Gly Ser Thr Thr Asn Asp Pro Pro Lys Gln Ser Pro Gly Ser Thr Ser
                     145
                                        150
Pro Lys Pro Pro His Thr Leu Ser Arg Lys Gln Trp Arg Asn Arg Gln
                 160
                                     165
Lys Asn Lys Arg Arg Cys Lys Asn Lys Phe Gln Pro Pro Gln Val Pro
                                 180
              175
Asp Gln Ala Pro Ala Glu Ala Pro Thr Glu Lys Thr Glu Val Ser Pro
           190
                             195
Val Pro Arg Thr Asp Ser His Gly Ala Arg Ala Gly Ala Leu Arg Ala
                      210
       205
Arg Met Ala Gln Arg Leu Asp Gly Ala Arg Phe Arg Tyr Leu Asn Glu
                                        230
                     225
Gln Leu Tyr Ser Gly Pro Ser Ser Ala Ala Gln Arg Leu Phe Gln Glu
                           245
                 240
Asp Pro Glu Ala Phe Leu Leu Tyr His Arg Gly Phe Gln Ser Gln Val
                                260
Lys Lys Trp Pro Leu Gln Pro Val Asp Arg Ile Ala Arg Asp Leu Arg
                             275
           270
                                                280
Gln Arg Pro Ala Ser Leu Val Val Ala Asp Phe Gly Cys Gly Asp Cys
                                             295
                          290
Arg Leu Ala Ser Ser Ile Arg Asn Pro Val His Cys Phe Asp Leu Ala
                      305
                                         310
Ser Leu Asp Pro Arg Val Thr Val Cys Asp Met Ala Gln Val Pro Leu
                                     325
                  320
Glu Asp Glu Ser Val Asp Val Ala Val Phe Cys Leu Ser Leu Met Gly
                                 340
               335
Thr Asn Ile Arg Asp Phe Leu Glu Glu Ala Asn Arg Val Leu Lys Pro
                              355
           350
Gly Gly Leu Leu Lys Val Ala Glu Val Ser Ser Arg Phe Glu Asp Val
                          370
                                            375
Arg Thr Phe Leu Arg Ala Val Thr Lys Leu Gly Phe Lys Ile Val Ser
                                        390
                      385
Lys Asp Leu Thr Asn Ser His Phe Phe Leu Phe Asp Phe Gln Lys Thr
                                    405
                  400
Gly Pro Pro Leu Val Gly Pro Lys Ala Gln Leu Ser Gly Leu Gln Leu
                                420
              415
Gln Pro Cys Leu Tyr Lys Arg Arg
           430
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<210> 209 <211> 98 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -17..-1

WO 99/31236 -148- PCT/IB98/02122 ...

<400> 209 Met Pro Ser Ser Phe Phe Leu Leu Gln Phe Phe Leu Arg Ile Asp -10 -5 Gly Val Leu Ile Arg Met Asn Asp Thr Arg Leu Tyr His Glu Ala Asp 10 5 Lys Thr Tyr Met Leu Arg Glu Tyr Thr Ser Arg Glu Ser Lys Ile Ser 25 20 Ser Leu Met His Val Pro Pro Ser Leu Phe Thr Glu Pro Asn Glu Ile 40 Ser Gln Tyr Leu Pro Ile Lys Glu Ala Val Cys Glu Lys Leu Ile Phe 55 50 Pro Glu Arg Ile Asp Pro Asn Pro Ala Asp Ser Gln Lys Ser Thr Gln 70 Val Glu 80 <210> 210 <211> 83 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -29..-1 <400> 210 Met Thr Leu Leu Ser Phe Ala Ala Phe Thr Ala Ala Phe Ser Val Leu -20 Pro Cys Tyr Tyr Leu Gly Leu Phe Gln Arg Ala Leu Ala Ser Val Phe -5 -10 Asp Pro Leu Cys Val Cys Ser Arg Val Leu Pro Thr Pro Val Cys Thr 10 Leu Val Ala Thr Gln Ala Glu Lys Ile Leu Glu Asn Gly Pro Cys Pro 25 30 Thr Lys Glu Ala Ala Gln Leu Val Gly Lys Gly Ser Val Ser Ala Arg 45 Asn Ala Ser <210> 211

Tyr Gln Pro Met Pro Leu Lys Ala Ser Leu Glu Ile Glu Tyr Gln Val
30 35 40
Leu Asp Gly Ala Gly Leu Asp Ile Asp Phe His Leu Ala Ser Pro Glu

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50
          45
Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr
                                          70
                  65
Val Glu Thr Glu Val Gly Asp Tyr Met Phe Cys Phe Asp Asn Thr Phe
                                      85
                     8.0
Ser Thr Ile Ser Glu Lys Val Ile Phe Phe Glu Leu Ile Leu Asp Asn
                                 100
                 95
Met Gly Glu Gln Ala Gln Glu Glu Asp Trp Lys Lys Tyr Ile Thr
                                                 120
                              115
             110
Gly Thr Asp Ile Leu Asp Met Lys Leu Glu Asp Ile Leu Glu Ser Ile
                                            135
                     130
          125
Ser Ser Ile Lys Ser Arg Leu Ser Lys Ser Gly His Ile Gln Ile Leu
                                        150
                      145
Leu Arg Ala Phe Glu Ala Arg Asp Arg Asn Ile Gln Glu Ser Asn Phe
              160
                                165
Asp Arg Val Asn Phe Trp Ser Met Val Asn Leu Val Val Met Val Val
                             180
        175
Val Ser Ala Ile Gln Val Tyr Met Leu Lys Ser Leu Phe Glu Asp Lys
                             195
             190
Arg Lys Ser Arg Thr
           205
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<210> 212 <211> 152 <212> PRT <213> Homo sapiens

<220>
<221> SIGNAL
<222> -21..-1

<400> 212 Met Ala Gln Leu Gly Ala Val Val Ala Val Ala Ser Ser Phe Phe Cys -10 -15 Ala Ser Leu Phe Ser Ala Val His Lys Ile Glu Glu Gly His Ile Gly 1 Val Tyr Tyr Arg Gly Gly Ala Leu Leu Thr Ser Thr Ser Gly Pro Gly 25 20 15 Phe His Leu Met Leu Pro Phe Ile Thr Ser Tyr Lys Ser Val Gln Thr 40 35 Thr Leu Gln Thr Asp Glu Val Lys Asn Val Pro Cys Gly Thr Ser Gly 55 Gly Val Met Ile Tyr Phe Asp Arg Ile Glu Val Val Asn Phe Leu Val 70 Pro Asn Ala Val His Asp Ile Val Lys Asn Tyr Thr Ala Asp Tyr Asp 85 Lys Ala Leu Ile Phe Asn Lys Ile His His Glu Leu Asn Gln Phe Cys 105 100 Ser Val His Thr Leu Gln Glu Val Tyr Ile Glu Leu Phe Gly Leu Glu 115 Asn Asp Phe Ser Gln Glu Ser Ser 125

<210> 213 <211> 179 <212> PRT <213> Homo sapiens WO 99/31236 -150- PCT/IB98/02122 -

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<220>
<221> SIGNAL
<222> -54..-1
<400> 213
Met Ala Ala Ser Glu Ala Ala Val Val Ser Ser Pro Ser Leu Lys Thr
                                  -45
Asp Thr Ser Pro Val Leu Glu Thr Ala Gly Thr Val Ala Ala Met Ala
                              -30
                                                -25
Ala Thr Pro Ser Ala Arg Ala Ala Ala Ala Val Val Ala Ala Ala Ala
   -20
                          -15
                                          -10
Arg Thr Gly Ser Glu Ala Arg Val Ser Lys Ala Ala Leu Ala Thr Lys
                                  5
Leu Leu Ser Leu Ser Gly Val Phe Ala Val His Lys Pro Lys Gly Pro
              15
                                 20
Thr Ser Ala Glu Leu Leu Asn Arg Leu Lys Glu Lys Leu Leu Ala Glu
                             35
Ala Gly Met Pro Ser Pro Glu Trp Thr Lys Arg Lys Lys Gln Thr Leu
                         50
Lys Ile Gly His Gly Gly Thr Leu Asp Ser Ala Ala Arg Gly Val Leu
                      65
                                        70
Val Val Gly Ile Gly Ser Gly Thr Lys Met Leu Thr Ser Met Leu Ser
                  80
                                     85
Gly Ser Lys Arg Tyr Thr Ala Ile Gly Glu Leu Gly Lys Ala Thr Asp
                                 100
              95
Thr Leu Asp Ser Thr Gly Lys Val Thr Glu Glu Lys Pro Tyr Gly Met
          110
                   115
Asn Leu Ile
      125
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<210> 214
<211> 269
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -92..-1
Met Ile Thr His Val Thr Leu Glu Asp Ala Leu Ser Asn Val Asp Leu
   -90
                          -85
                                              -80
Leu Glu Glu Leu Pro Leu Pro Asp Gln Gln Pro Cys Ile Glu Pro Pro
                      -70
                                         -65
Pro Ser Ser Ile Met Tyr Gln Ala Asn Phe Asp Thr Asn Phe Glu Asp
                  -55 · -50
Arg Asn Ala Phe Val Thr Gly Ile Ala Arg Tyr Ile Glu Gln Ala Thr
              -40
                                  -35
Val His Ser Ser Met Asn Glu Met Leu Glu Glu Gly His Glu Tyr Ala
                              -20
                                                 -15
Val Met Leu Tyr Thr Trp Arg Ser Cys Ser Arg Ala Ile Pro Gln Val
                          -5
Lys Cys Asn Glu Gln Pro Asn Arg Val Glu Ile Tyr Glu Lys Thr Val
                  10
                                     15
Glu Val Leu Glu Pro Glu Val Thr Lys Leu Met Lys Phe Met Tyr Phe
               25
                                  30
Gln Arg Lys Ala Ile Glu Arg Phe Cys Ser Glu Val Lys Arg Leu Cys
                              45
```

His Ala Glu Arg Arg Lys Asp Phe Val Ser Glu Ala Tyr Leu Leu Thr
55 60 65

Leu Gly Lys Phe Ile Asn Met Phe Ala Val Leu Asp Glu Leu Lys Asn 75 Met Lys Cys Ser Val Lys Asn Asp His Ser Ala Tyr Lys Arg Ala Ala 90 95 Gln Phe Leu Arg Lys Met Ala Asp Pro Gln Ser Ile Gln Glu Ser Gln 105 110 Asn Leu Ser Met Phe Leu Ala Asn His Asn Arg Ile Thr Gln Cys Leu 120 125 His Gln Gln Leu Glu Val Ile Pro Gly Tyr Glu Glu Leu Leu Ala Asp 140 145 Ile Val Asn Ile Cys Val Asp Tyr Tyr Glu Asn Lys Met Tyr Leu Thr 155 160 Pro Ser Glu Lys His Met Leu Leu Lys Val Lys Leu Pro 170 175

<210> 215
<211> 135
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -22..-1

<400> 215 Met Gln Thr Val Tyr Tyr Gly Ser Leu Gly Leu Trp Leu Ala Leu Val -20 -15 Asp Gly Leu Val Arg Ser Ser Pro Ser Leu Asp Gln Met Phe Asp Ala 1 . Glu Ile Leu Gly Phe Ser Thr Pro Pro Gly Arg Leu Ser Met Met Ser 20 15 Phe Ile Phe Asn Ala Leu Thr Cys Ala Leu Gly Leu Leu Tyr Phe Ile 35 Arg Arg Gly Lys Gln Cys Leu Asp Phe Thr Val Thr Val His Phe Phe 50 His Leu Leu Gly Cys Trp Phe Tyr Ser Ser Arg Phe Pro Ser Ala Leu 65 70 Thr Trp Trp Leu Val Gln Ala Val Cys Ile Ala Leu Met Ala Val Ile 85 80 Gly Glu Tyr Leu Cys Met Arg Thr Glu Leu Lys Glu Ile Pro Leu Asn 95 100

<210 > 216 <211 > 67 <212 > PRT <213 > Homo sapiens <220 > <221 > SIGNAL <222 > -38..-1

Ser Ala Pro Lys Ser Asn Val 110

WO 99/31236 -152 - PCT/IB98/02122 -

Ala Val Cys Cys Leu Ala Asp Gly Ala Leu Ile Tyr Arg Lys Leu Leu -5 1 5 10

Phe Asn Pro Asn Gly Pro Tyr Gln Lys Lys Pro Val His Glu Lys Lys Lys Glu Val Leu 25

<210> 217 <211> 125 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -54..-1 <400> 217 Met Ala Asp Glu Glu Leu Glu Ala Leu Arg Arg Gln Arg Leu Ala Glu -50 -45 Leu Gln Ala Lys His Gly Asp Pro Gly Asp Ala Ala Gln Glu Ala -25 -30 -35 Lys His Arg Glu Ala Glu Met Arg Asn Ser Ile Leu Ala Gln Val Leu -15 Asp Gln Ser Ala Arg Ala Arg Leu Ser Asn Leu Ala Leu Val Lys Pro Glu Lys Thr Lys Ala Val Glu Asn Tyr Leu Ile Gln Met Ala Arg Tyr 20 Gly Gln Leu Ser Glu Lys Val Ser Glu Gln Gly Leu Ile Glu Ile Leu 35 Lys Lys Val Ser Gln Gln Thr Glu Lys Thr Thr Thr Val Lys Phe Asn 50

Arg Arg Lys Val Met Asp Ser Asp Glu Asp Asp Asp Tyr

<210> 218 <211> 376 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 <400> 218 Met Gly His Arg Phe Leu Arg Gly Leu Leu Thr Leu Leu Pro Pro -15 -10 Pro Pro Leu Tyr Thr Arg His Arg Met Leu Gly Pro Glu Ser Val Pro Pro Pro Lys Arg Ser Arg Ser Lys Leu Met Ala Pro Pro Arg Ile Gly 20 Thr His Asn Gly Thr Phe His Cys Asp Glu Ala Leu Ala Cys Ala Leu 35 40 Leu Arg Leu Leu Pro Glu Tyr Arg Asp Ala Glu Ile Val Arg Thr Arg 50 55 Asp Pro Glu Lys Leu Ala Ser Cys Asp Ile Val Val Asp Val Gly Gly 70 65 Glu Tyr Asp Pro Arg Arg His Arg Tyr Asp His His Gln Arg Ser Phe 85 Thr Glu Thr Met Ser Ser Leu Ser Pro Gly Arg Pro Trp Gln Thr Lys

100 105 Leu Ser Ser Ala Gly Leu Ile Tyr Leu His Phe Gly His Lys Leu Leu 110 115 . 120 Ala Gln Leu Cly Thr Ser Glu Glu Asp Ser Met Val Gly Thr Leu 130 135 Tyr Asp Lys Met Tyr Glu Asn Phe Val Glu Glu Val Asp Ala Val Asp 145 150 Asn Gly Ile Ser Gln Trp Ala Glu Gly Glu Pro Arg Tyr Ala Leu Thr 165 Thr Thr Leu Ser Ala Arg Val Ala Arg Leu Asn Pro Thr Trp Asn His 180 185 175 Pro Asp Gln Asp Thr Glu Ala Gly Phe Lys Arg Ala Met Asp Leu Val 200 195 Gln Glu Glu Phe Leu Gln Arg Leu Asp Phe Tyr Gln His Ser Trp Leu 210 215 Pro Ala Arg Ala Leu Val Glu Glu Ala Leu Ala Gln Arg Phe Gln Val 230 225 Asp Pro Ser Gly Glu Ile Val Glu Leu Ala Lys Gly Ala Cys Pro Trp 240 245 Lys Glu His Leu Tyr His Leu Glu Ser Gly Leu Ser Pro Pro Val Ala 260 Ile Phe Phe Val Ile Tyr Thr Asp Gln Ala Gly Gln Trp Arg Ile Gln 280 275 Cys Val Pro Lys Glu Pro His Ser Phe Gln Ser Arg Leu Pro Leu Pro 290 295 Glu Pro Trp Arg Gly Leu Arg Asp Glu Ala Leu Asp Gln Val Ser Gly 305 310 Ile Pro Gly Cys Ile Phe Val His Ala Ser Gly Phe Ile Gly Gly His 325 .. 330 320 Arg Thr Arg Glu Gly Ala Leu Ser Met Ala Arg Ala Thr Leu Ala Gln 335 340 Arg Ser Tyr Leu Pro Gln Ile Ser 350

<210> 219 <211> 211 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<400> 219

<222> -30..-1

Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arg Arg His Leu Leu Val -30 -25 -20 Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Pro -10 - 5 Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu 10 Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys Gly Asn Leu 25 Leu Arg Gly Ile Asp Ser Leu Phe Ser Ala Pro Met Asp Phe Arg Gly 40 45 Leu Pro Gly Asn Tyr His Lys Glu Glu Asn Gln Glu His Gln Leu Gly 55 60 Asn Asn Thr Leu Ser Ser His Leu Gln Ile Asp Lys Val Pro Arg Met 75 Glu Glu Lys Glu Ala Leu Val Pro Ile Gln Lys Ala Thr Asp Ser Phe 90

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His Thr Glu Leu His Pro Arg Val Ala Phe Trp Ile Ile Lys Leu Pro
                     105
Arg Arg Arg Ser His Gln Asp Ala Leu Glu Gly Gly His Trp Leu Ser
                                    125
                 120
Glu Lys Arg His Arg Leu Gln Ala Ile Arg Asp Gly Leu Arg Lys Gly
                                140
              135
Thr His Lys Asp Val Leu Glu Glu Gly Thr Glu Ser Ser His Ser
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         150
Arg Leu Ser Pro Arg Lys Thr His Leu Leu Tyr Ile Leu Arg Pro Ser
                 170
Arg Gln Leu
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<210> 220 <211> 154 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -60..-1

<400> 220

Met Gly Ser Lys Cys Cys Lys Gly Gly Pro Asp Glu Asp Ala Val Glu -50 -55 Arg Gln Arg Arg Gln Lys Leu Leu Leu Ala Gln Leu His His Arg Lys -40 -35 Arg Val Lys Ala Ala Gly Gln Ile Gln Ala Trp Trp Arg Gly Val Leu -20 -15 Val Arg Arg Thr Leu Leu Val Ala Ala Leu Arg Ala Trp Met Ile Gln -10 -5 Cys Trp Trp Arg Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln 15 10 Ala Leu Leu Arg Val Tyr Val Ile Gln Glu Gln Ala Thr Val Lys Leu 25 30 Gln Ser Cys Ile Arg Met Trp Gln Cys Arg Gln Cys Tyr Arg Gln Met 45

Cys Asn Ala Leu Cys Leu Phe Gln Val Pro Glu Ser Ser Leu Ala Phe 60 65 Gln Thr Asp Gly Phe Leu Gln Val Gln Tyr Ala Ile Pro Ser Lys Gln 75

Pro Glu Phe His Ile Glu Ile Leu Ser Ile 90

<210> 221 <211> 123 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -42..-1 <400> 221

Met Lys Gly Gly Ala Phe Ser Asn Leu Asn Asp Ser Gln Leu Ser Ala -35 -30 Ser Phe Leu Gln Pro Ser Leu Gln Ala Asn Cys Pro Ala Leu Asp Pro -25 -15 -20

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<210> 222 <211> 346 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -19..-1

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Gln Leu Glu Ala Val Ala Leu Asp Tyr Glu Ala Arg Arg Pro Ile Tyr

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                                     -10
Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp
Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys
       15
                          20
Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr
Asn Asp Ala Leu Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Arg Arg
                   50
Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg
              65
                                  70
Thr Glu Ser Phe Asp Val Val Thr Lys Cys Val Ser Phe Thr Leu Thr
           80
                              85
Glu Gln Phe Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly
                          100
Ile Asp Leu Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro
                      115
Phe Val Ser Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys
                 130
                                     135
Ala Cys Ile Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu
                       150
              145
His Leu Leu Ala Val Thr Lys Glu Ser Met Leu Pro Ala Gly Ala Glu
                             165
                                                170
Ser Lys His Thr Ala Thr Pro Ala His Ala Cys Val Gln Thr Gly Lys
                          180
Pro Lys
  190
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Met Asp Asn Arg Phe Ala Thr Ala Phe Val Ile Ala Cys Val Leu Ser

-15 -10 Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp 1 5 . 10 Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys 20 Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr 35 Asn Asp Ala Pro Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Arg Arg 50 55 Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg 70 Thr Glu Ser Phe Asp Val Val Thr Lys Cys Val Ser Phe Thr Leu Thr 85 90 Glu Gln Phe Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly 100 105 Ile Asp Leu Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro 115 120 Phe Val Ser Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys 130 135 Ala Cys Ile Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu 145 150 His Leu Leu Ala Asp Thr Met Leu 160

<210> 225 <211> 227 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -22..-1

<400> 225

Met Gly Trp Thr Met Arg Leu Val Thr Ala Ala Leu Leu Leu Gly Leu -15 Met Met Val Val Thr Gly Asp Glu Asp Glu Asn Ser Pro Cys Ala His 1 Glu Ala Leu Leu Asp Glu Asp Thr Leu Phe Cys Gln Gly Leu Glu Val 15 20 Phe Tyr Pro Glu Leu Gly Asn Ile Gly Cys Lys Val Val Pro Asp Cys 35 Asn Asn Tyr Arg Gln Lys Ile Thr Ser Trp Met Glu Pro Ile Val Lys 50 Phe Pro Gly Ala Val Asp Gly Ala Thr Tyr Ile Leu Val Met Val Asp Pro Asp Ala Pro Ser Arg Ala Glu Pro Arg Gln Arg Phe Trp Arg His 85 80 Trp Leu Val Thr Asp Ile Lys Gly Ala Asp Leu Lys Lys Gly Lys Ile 95 100 Gln Gly Gln Glu Leu Ser Ala Tyr Gln Ala Pro Ser Pro Pro Ala His 110 115 Ser Gly Phe His Arg Tyr Gln Phe Phe Val Tyr Leu Gln Glu Gly Lys 130 Val Ile Ser Leu Leu Pro Lys Glu Asn Lys Thr Arg Gly Ser Trp Lys 145 Met Asp Arg Phe Leu Asn Arg Phe His Leu Gly Glu Pro Glu Ala Ser

Thr Gln Phe Met Thr Gln Asn Tyr Gln Asp Ser Pro Thr Leu Gln Ala

180

155 160 165

Pro Arg Glu Arg Ala Ser Glu Pro Lys His Lys Asn Gln Ala Glu Ile 190 195 Ala Ala Cys 205

<210> 226 <211> 74 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -41..-1

<400> 226

Met Ile Ala Arg Arg Asn Pro Val Pro Leu Arg Phe Leu Pro Asp Glu -35 -30 Ala Arg Ser Leu Pro Pro Pro Lys Leu Thr Asp Pro Arg Leu Leu Tyr -20 -15 Ile Gly Phe Leu Gly Tyr Cys Ser Gly Leu Ile Asp Asn Leu Ile Arg -5 5 1 Arg Arg Pro Ile Ala Thr Ala Gly Leu His Arg Gln Leu Leu Tyr Ile 10 15 Thr Ala Phe Phe Leu Leu Asp Ile Ile Leu

<210> 227 <211> 73 <212> PRT <213> Homo sapiens <400> 227 Met Glu Lys Tyr Glu Asn Leu Gly Leu Val Gly Glu Gly Ser Tyr Gly 10 Met Val Met Lys Cys Arg Asn Lys Asp Thr Gly Arg Ile Val Ala Ile 20 25 Lys Lys Phe Leu Glu Ser Asp Asp Lys Met Val Lys Lys Ile Ala 40 45 Met Arg Glu Val Lys Leu Leu Lys Gln Leu Arg His Glu Asn Leu Val

Asn Leu Leu Glu Val Cys Lys Lys 70

<210> 228 <211> 82 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -16..-1

<400> 228 Met Lys Arg Leu Leu Pro Ala Thr Ser Leu Ala Gly Pro Val Leu Ser -10 - 5 Thr Leu Ile Ala Pro Thr Pro Met Leu Phe Cys Glu Asp Lys Ser Trp

<210> 229 <211> 119 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -56..-1 <400> 229 Met Ala Glu Pro Ser Ala Ala Thr Gln Ser His Ser Ile Ser Ser Ser -50 -45 Ser Phe Gly Ala Glu Pro Ser Ala Pro Gly Gly Gly Ser Pro Gly -35 -30 Ala Cys Pro Ala Leu Gly Thr Lys Ser Cys Ser Ser Ser Cys Ala Asp -20 -15 Ser Phe Val Ser Ser Ser Ser Gln Pro Val Ser Leu Phe Ser Thr -5 1 Ser Gln Glu Gly Leu Ser Ser Leu Cys Ser Asp Glu Pro Ser Ser Glu 15 20 Ile Met Thr Ser Ser Phe Leu Ser Ser Ser Glu Ile His Asn Thr Gly 30 35

Leu Thr Ile Leu His Gly Glu Lys Ser His Val Leu Gly Ser Gln Pro

<210> 230 <211> 54 <212> PRT <213> Homo sapiens

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Ile Leu Ala Lys Lys Lys 60

Ala Phe Val Trp Glu Pro Ala Met Val Arg Ile Asn Ala Leu Thr Ala 1 5 10 15 15

Ala Ser Glu Ala Ala Cys Leu Ile Val Ser Val Asp Glu Thr Ile Lys 20 25 30

Asn Pro Arg Ser Thr Val Asp Ala Pro Thr Ala Ala Gly Arg Gly Arg Gly Arg Gly Arg Gly Arg 50

Gly Arg Gly Arg Pro His 50

<210> 231 <211> 210 <212> PRT <213> Homo sapiens

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              -10
                              -5
Gly Gly Ala Cys Ile Tyr Lys Tyr Phe Met Pro Lys Ser Thr Ile Tyr
                          10
                                       15
Arg Gly Glu Met Cys Phe Phe Asp Ser Glu Asp Pro Ala Asn Ser Leu
                                         30
Arg Gly Glu Pro Asn Phe Leu Pro Val Thr Glu Glu Ala Asp Ile
                   40
Arg Glu Asp Asp Asn Ile Ala Ile Ile Asp Val Pro Val Pro Ser Phe
                                 60
Ser Asp Ser Asp Pro Ala Ala Ile Ile His Asp Phe Glu Lys Gly Met
          70
                              75
Thr Ala Tyr Leu Asp Leu Leu Gly Ile Cys Tyr Leu Met Pro Leu
                          90
Asn Thr Ser Ile Val Met Pro Pro Lys Asn Leu Val Glu Leu Phe Gly
                      105
                                        110
Lys Leu Ala Ser Gly Arg Tyr Leu Pro Gln Thr Tyr Val Val Arg Glu
                  120
                                     125
Asp Leu Val Ala Val Glu Glu Ile Arg Asp Val Ser Asn Leu Gly Ile
                                 140
              135
Phe Ile Tyr Gln Leu Cys Asn Asn Arg Lys Ser Phe Arg Leu Arg Arg
           150
                             155
Arg Asp Leu Leu Gly Phe Asn Lys Arg Ala Ile Asp Lys Cys Trp
                         170
                                             175
Lys Ile Arg His Phe Pro Asn Glu Phe Ile Val Glu Thr Lys Ile Cys
            185
Gln Glu
195
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<210> 232 <211> 108 <212> PRT <213> Homo sapiens

<400> 232

 Met
 Gly
 Cys
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 Phe
 Gln
 Ser
 Thr
 Glu
 Asp
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 Phe
 Lys
 Ile

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<210> 233 <211> 43

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<222> -18..-1
<400> 233
Met Ser Ser Gly Arg Leu Arg Trp Leu Met Pro Val Ile Pro Ala Leu
                               -10
Trp Gly Ala Glu Lys Gly Glu Ser Pro Glu Val Ser Ser Phe Glu Thr
      1
Arg Leu Ala Asn Met Ala Lys Pro Cys Leu Tyr
15 20
<210> 234
<211> 36
<212> PRT
<213> Homo sapiens
<400> 234
Met Ser Ala Arg Ile Pro Phe Tyr Lys Asp Thr Ser Gln Ile Arg Leu
                                   10
Gly Ser Thr Ile Ile Pro His Phe Asn Leu Ile Thr Phe Val Lys Thr
          20
                               25
Phe Phe Gln Ile
       35
<210> 235
<211> 307
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -13..-1
<400> 235
Met Leu Ala Val Ser Leu Thr Val Pro Leu Leu Gly Ala Met Met Leu
           -10
                           -5
Leu Glu Ser Pro Ile Asp Pro Gln Pro Leu Ser Phe Lys Glu Pro Pro
                       10
Leu Leu Gly Val Leu His Pro Asn Thr Lys Leu Arg Gln Ala Glu
                   25
                                       30
Arg Leu Phe Glu Asn Gln Leu Val Gly Pro Glu Ser Ile Ala His Ile
                                   45
Gly Asp Val Met Phe Thr Gly Thr Ala Asp Gly Arg Val Val Lys Leu
                               60
Glu Asn Gly Glu Ile Glu Thr Ile Ala Arg Phe Gly Ser Gly Pro Cys
                           75
Lys Thr Arg Asp Asp Glu Pro Val Cys Gly Arg Pro Leu Gly Ile Arg
                       90
                                           95
Ala Gly Pro Asn Gly Thr Leu Phe Val Ala Asp Ala Cys Lys Gly Leu
                   105
                                       110
Phe Glu Val Asn Pro Trp Lys Arg Glu Val Lys Leu Leu Ser Ser
               120
                                  125
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Glu Thr Pro Ile Glu Gly Lys Asn Met Ser Phe Val Asn Asp Leu Thr

140

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Val Ser Gln Asp Gly Arg Lys Ile Tyr Phe Thr Asp Ser Ser Ser Lys 155 Trp Gln Arg Arg Asp Tyr Leu Leu Leu Val Met Glu Gly Thr Asp Asp 170 175 Gly Arg Leu Leu Glu Tyr Asp Thr Val Thr Arg Glu Val Lys Val Leu 180 185 190 Leu Asp Gln Leu Arg Phe Pro Asn Gly Val Gln Leu Ser Pro Ala Glu 200 205 Asp Phe Val Leu Val Ala Glu Thr Thr Met Ala Arg Ile Arg Arg Val 220 225 Tyr Val Ser Gly Leu Met Lys Gly Gly Ala Asp Leu Phe Val Glu Asn 235 240 Met Pro Gly Phe Pro Asp Asn Ile Arg Pro Ser Ser Ser Gly Gly Tyr 250 255 Trp Val Gly Met Ser Thr Ile Arg Pro Asn Pro Gly Phe Ser Met Leu 265 270 Asp Phe Leu Ser Glu Arg Pro Trp Ile Lys Arg Met Ile Phe Lys Ala 285 Lys Lys Lys

<210> 236 <211> 106 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -32..-1

<400> 236 Met Phe Ala Pro Ala Val Met Arg Ala Phe Arg Lys Asn Lys Thr Leu -30 -25 Gly Tyr Gly Val Pro Met Leu Leu Leu Ile Val Gly Gly Ser Phe Gly -15 -10 - 5 Leu Arg Glu Phe Ser Gln Ile Arg Tyr Asp Ala Val Lys Ser Lys Met 10 Asp Pro Glu Leu Glu Lys Lys Leu Lys Glu Asn Lys Ile Ser Leu Glu 20 25 Ser Glu Tyr Glu Lys Ile Lys Asp Ser Lys Phe Asp Asp Trp Lys Asn 35 40 45 Ile Arg Gly Pro Arg Pro Trp Glu Asp Pro Asp Leu Leu Gln Gly Arg 55 Asn Pro Glu Ser Leu Lys Thr Lys Thr Thr

70

<210> 237 <211> 42 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -19..-1

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Gln Leu Ser Asp Lys Val His Asn Asp Ile
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<400> 238
Met Asp Asn Arg Phe Ala Thr Ala Phe Val Ile Ala Cys Val Leu Ser
                -15
                                      -10
Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp
Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys
                           20
Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr
Asn Asp Ala Leu Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Gly Arg
               50
                               .... 55
Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg
                                  70
Thr Gly Ile Ser Leu Ile Leu Thr Ser Val Phe Phe Thr Trp Leu Ile
        80
                           85
Ile Asp Lys Thr Thr
      95
<210> 239
<211> 178
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<400> 239
Met Glu Arg Gln Ser Arg Val Met Ser Glu Lys Asp Glu Tyr Gln Phe
      -35
                         -30
                                              -25
Gln His Xaa Xaa Ala Xaa Xaa Leu Leu Val Phe Asn Phe Leu Leu Ile
                       -15
                                         -10
Leu Thr Ile Leu Thr Ile Trp Leu Phe Lys Asn His Arg Phe Arg Phe
Leu His Glu Thr Gly Gly Ala Met Val Tyr Gly Leu Ile Met Gly Leu
                               20
Ile Ser Arg Tyr Ala Thr Ala Pro Thr Asp Ile Glu Ser Gly Thr Val
                           35
Cys Asp Cys Val Lys Leu Thr Phe Ser Pro Pro Thr Leu Leu Val Asn
                       50
Val Thr Asp Gln Val Tyr Glu Tyr Lys Tyr Lys Arg Glu Ile Ser Gln
                  65
                                      70
His Asn Ile Asn Pro His Gln Gly Asn Ala Ile Leu Glu Lys Met Thr
```

85

Phe Asp Pro Glu Ile Phe Phe Asn Val Leu Leu Pro Pro Ile Ile Phe

WO 99/31236 -164 - PCT/IB98/02122

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100
His Ala Gly Tyr Ser Leu Lys Lys Arg His Phe Phe Gln Asn Leu Gly
 110 115
Ser Ile Leu Thr Tyr Ala Phe Leu Gly Thr Ala Ile Ser Cys Ile Val
                    130
Ile Gly
140
<210> 240
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<400> 240
Met Gln Phe Val Asn Val Gly Tyr Phe Leu Ile Ala Ala Gly Val Val
                         -20
Val Leu Ala Leu Gly Phe Leu Gly Cys Tyr Gly Ala Lys Thr Glu Ser
                      -5
                                        1
Met Cys Ala Leu Val Thr Phe Phe Ile Leu Leu Ile Phe Ile
              10
                                  15
Ala Glu Val Ala Ala Ala Val Val Ala Leu Val Tyr Thr Thr Met Ala
                              30
Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys Asp Tyr
                          45
Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met Lys Gly
                       60
Leu Lys Cys Arg Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp Ser Pro
                   75
Tyr Phe Lys Met His Lys Pro Val Thr Met Lys Lys Lys
              90
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<211> 174
<212> PRT
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<400> 241
Met Arg Trp Ser Cys Glu His Leu Val Met Val Trp Ile Asn Ala Phe
                  -110
                                      -105
Val Met Leu Thr Thr Gln Leu Leu Pro Ser Lys Tyr Cys Asp Leu Leu
              -95
                                  -90
His Lys Ser Ala Ala His Leu Gly Lys Trp Gln Lys Leu Glu His Gly
                              -75
                                                 -70
Ser Tyr Ser Asn Ala Pro Gln His Ile Trp Ser Glu Asn Thr Ile Trp
                          -60
                                             -55
Pro Gln Gly Val Leu Val Arg His Ser Arg Cys Leu Tyr Arg Ala Met
                      -45
Gly Pro Tyr Asn Val Ala Val Pro Ser Asp Val Ser His Ala Arg Phe
                  -30
                                      -25
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Tyr Phe Leu Phe His Arg Pro Leu Arg Leu Leu Asn Leu Leu Ile Leu

-10

- 5

613

673

733

793

853

-15

Ile Glu Gly Gly Val Val Phe Tyr Gln Leu Tyr Ser Leu Leu Arg Ser. 5 Glu Lys Trp Asn His Thr Leu Ser Met Ala Leu Ile Leu Phe Cys Asn 15 20 Tyr Tyr Val Leu Phe Lys Leu Leu Arg Asp Arg Ile Val Leu Gly Arg 30 35 40 Ala Tyr Ser Tyr Pro Leu Asn Ser Tyr Glu Leu Lys Ala Asn <210> 242 <211> 896 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 18..173 <221> sig_peptide <222> 18..77 <223> Von Heijne matrix score 6.5 seq GLCVLQLTTAVTS/AF <221> polyA signal <222> 864..869 <221> polyA site <222> 882..893 <400> 242 aaccttcaca gtgtgag atg cct agt gtg aac agt gct gga tta tgt gtc 50 Met Pro Ser Val Asn Ser Ala Gly Leu Cys Val -20 -15 ttg cag ttg aca acg gca gtr acc agt gcc ttt tta cta gca aaa gtg 98 Leu Gln Leu Thr Thr Ala Val Thr Ser Ala Phe Leu Leu Ala Lys Val -5 1 aat eet tte gaa ret ttt ete tea agg gge ttt tgg eta tgt get gee 146 Asn Pro Phe Glu Xaa Phe Leu Ser Arg Gly Phe Trp Leu Cys Ala Ala 15 cat cat ttc att cat cct tgc ctg gat tgagacgtgt tcctgattca 193 His His Phe Ile His Pro Cys Leu Asp 30 aagtgttacc tcaagaagca gaagaagaaa acagactcct gatagttcag gatgcttcag agagggcagc acttatacct ggtggtcttt ctgatggtca gttttattcc cctcctgaat 313 ccgaagcagg atctgaagaa gctgaagaaa aacaggacag tgagaaacca cttttagaac 373 tatgagtact acttttgtta aatgtgaaaa accctcacag aaagtcatcg aggcaaaaaag aggcaggcag tggagtctcc ctgtcgacag taaagttgaa atggtgacgt ccactgctgg ctttattgaa cagctaataa agatttattt attgtaatac ctcacagacg ttgtaccata

tccatgcaca tttagttgcc tgcctgtggc tggtaaggta atgtcatgat tcatcctctc

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ctaatcaaaa gacttaatat attgaagtaa cactttttta gtaagcaaga taccttttta

tttcaattca cagaatggaa tttttttgtt tcatgtctca gatttatttt gtatttcttt

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taaaaagtgt aataaaatct gacatgtcaa araaaaaaaa mcy

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      seq FLPPLXRAFACRG/CQ
<221> polyA_signal
<222> 820..825
<221> polyA_site
<222> 840..851
<400> 243
aagggggcgt ggggcc atg gtg gtc ttg cgg gcg ggg aag aag acc ttt ctc
                                                                       52
                  Met Val Val Leu Arg Ala Gly Lys Lys Thr Phe Leu
                              -20
                                                  -15
ccc cct ctm wgc cgc gcc ttc gcc tgc cgc ggc tgt caa ctc gct ccg
                                                                      100
Pro Pro Leu Xaa Arg Ala Phe Ala Cys Arg Gly Cys Gln Leu Ala Pro
                        -5
gag cgc ggc gcc gag cgc agg gat aca gcg ccc agc ggg gtc tca aga
                                                                      148
Glu Arg Gly Ala Glu Arg Arg Asp Thr Ala Pro Ser Gly Val Ser Arg
                10
                                    15
ttc tgc cct cca aga aag tct tgc cat gat tgg ata gga ccc cca gat
                                                                      196
Phe Cys Pro Pro Arg Lys Ser Cys His Asp Trp Ile Gly Pro Pro Asp
                                30
aaa tat tca aac ctt cga cct gtt cac ttt tac ata cct gaa aat gaa
                                                                      244
Lys Tyr Ser Asn Leu Arg Pro Val His Phe Tyr Ile Pro Glu Asn Glu
                            45
tct cca ttg gaa caa aag ctt aga aaa tta aga caa gaa aca caa gaa
                                                                      292
Ser Pro Leu Glu Gln Lys Leu Arg Lys Leu Arg Gln Glu Thr Gln Glu
                                            65
tgg aat caa cag ttc tgg gca aac cag aat ttg act ttt agt aag gaa
Trp Asn Gln Gln Phe Trp Ala Asn Gln Asn Leu Thr Phe Ser Lys Glu
70
                   75
aaa gaa gaa ttt att cac tca aga cta aaa act aaa ggc ctg ggc ctg
                                                                      388
Lys Glu Glu Phe Ile His Ser Arg Leu Lys Thr Lys Gly Leu Gly Leu
                90
                                    95
aga act gaa tca ggt cag aaa gca aca ttg aat gca gaa gaa atg gcg
                                                                      436
Arg Thr Glu Ser Gly Gln Lys Ala Thr Leu Asn Ala Glu Glu Met Ala
            105
                                110
gac ttc tac aag gaa ttt tta agt aaa aat ttt cag aag cac atg tat
                                                                      484
Asp Phe Tyr Lys Glu Phe Leu Ser Lys Asn Phe Gln Lys His Met Tyr
        120
                            125
tat aac aga gat tgg tac aag cgc aat ttt gcc atc acc ttc ttc atg
Tyr Asn Arg Asp Trp Tyr Lys Arg Asn Phe Ala Ile Thr Phe Phe Met
                        140
gga aaa gtg gcc ctg gaa agg att tgg aac aag ctt aaa cag aaa caa
                                                                      580
Gly Lys Val Ala Leu Glu Arg Ile Trp Asn Lys Leu Lys Gln Lys Gln
                                        160
aag aag agg agc aac taggagtcca ctctgaccca gccagagtcc aggtttccac
                                                                      635
Lys Lys Arg Ser Asn
                170
aggaagcara tggagctcct ttcacagggg ctctgagaaa aactggagct gatctcaaga
                                                                      695
agecccacat cttcctaagg ggccccatgg cctgtttggg ggcagggtag gtcctggggc
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	Phe Thr Leu Xaa Ser Leu
	Phe Thr Leu Xaa Ser Leu -10 atc gca gtg ctg cac gag 160
Ctg cag gca gcc ctg ctc tgc gtc aac gcc Leu Gln Ala Ala Leu Leu Cys Val Asn Ala -5 gag cga ttc ctc aag aac att ggc tgg gga Glu Arg Phe Leu Lys Asn Ile Gly Trp Gly	Phe Thr Leu Xaa Ser Leu -10 atc gca gtg ctg cac gag 160 Ile Ala Val Leu His Glu 5 10 aca gac cag gga att ggt 208 Thr Asp Gln Gly Ile Gly
Ctg Cag gca gcc ctg ctc tgc gtc aac gcc Leu Gln Ala Ala Leu Leu Cys Val Asn Ala -5 gag cga ttc ctc aag aac att ggc tgg gga Glu Arg Phe Leu Lys Asn Ile Gly Trp Gly 15 gga ttt gga gaa gag ccg gga att aaa tca Gly Phe Gly Glu Glu Pro Gly Ile Lys Ser	Phe Thr Leu Xaa Ser Leu -10 atc gca gtg ctg cac gag 160 Ile Ala Val Leu His Glu 5 10 aca gac cag gga att ggt 208 Thr Asp Gln Gly Ile Gly 25 sag sta atg avs ctt att 256 Xaa Xaa Met Xaa Leu Ile 40
ctg cag gca gcc ctg ctc tgc gtc aac gcc Leu Gln Ala Ala Leu Leu Cys Val Asn Ala -5 gag cga ttc ctc aag aac att ggc tgg gga Glu Arg Phe Leu Lys Asn Ile Gly Trp Gly 15 gga ttt gga gaa gag ccg gga att aaa tca Gly Phe Gly Glu Glu Pro Gly Ile Lys Ser 30 cga tct gta aga acc gtg atg aga gtg cca Arg Ser Val Arg Thr Val Met Arg Val Pro	Phe Thr Leu Xaa Ser Leu -10 atc gca gtg ctg cac gag 160 Ile Ala Val Leu His Glu 5 10 aca gac cag gga att ggt 208 Thr Asp Gln Gly Ile Gly 25 sag sta atg avs ctt att 256 Xaa Xaa Met Xaa Leu Ile 40 ttg ata ata gta aac tca 304 Leu Ile Ile Val Asn Ser
ctg cag gca gcc ctg ctc tgc gtc aac gcc Leu Gln Ala Ala Leu Leu Cys Val Asn Ala -5 gag cga ttc ctc aag aac att ggc tgg gga Glu Arg Phe Leu Lys Asn Ile Gly Trp Gly 15 gga ttt gga gaa gag ccg gga att aaa tca Gly Phe Gly Glu Glu Pro Gly Ile Lys Ser 30 gga tct gta aga acc gtg atg aga gtg cca	Phe Thr Leu Xaa Ser Leu -10 atc gca gtg ctg cac gag 160 Ile Ala Val Leu His Glu 5 10 aca gac cag gga att ggt 208 Thr Asp Gln Gly Ile Gly 25 sag sta atg avs ctt att 256 Xaa Xaa Met Xaa Leu Ile 40 ttg ata ata gta aac tca 304 Leu Ile Ile Val Asn Ser
ctg cag gca gcc ctg ctc tgc gtc aac gcc Leu Gln Ala Ala Leu Leu Cys Val Asn Ala -5 gag cga ttc ctc aag aac att ggc tgg gga Glu Arg Phe Leu Lys Asn Ile Gly Trp Gly 15 gga ttt gga gaa gag ccg gga att aaa tca Gly Phe Gly Glu Glu Pro Gly Ile Lys Ser 30 cga tct gta aga acc gtg atg aga gtg cca Arg Ser Val Arg Thr Val Met Arg Val Pro 45 att gca att gtg tta ctt tta tta ttt gga Ile Ala Ile Val Leu Leu Leu Leu Phe Gly	Phe Thr Leu Xaa Ser Leu -10 atc gca gtg ctg cac gag 160 Ile Ala Val Leu His Glu 5 10 aca gac cag gga att ggt 208 Thr Asp Gln Gly Ile Gly 25 sag sta atg avs ctt att 256 Xaa Xaa Met Xaa Leu Ile 40 ttg ata ata gta aac tca 304 Leu Ile Ile Val Asn Ser 55 tgaatwtcat tggagaaaat 354

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884

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                                                                   60
aggegeetge agg atg aaa get ete tgt ete ete ete eet gte etg
                                                                  109
              Met Lys Ala Leu Cys Leu Leu Leu Pro Val Leu
                         -15
ggg ctg ttg gtg tct agc aag acc ctg tgc tcc atg gaa gaa gcc atc
                                                                  157
Gly Leu Leu Val Ser Ser Lys Thr Leu Cys Ser Met Glu Glu Ala Ile
                      1
                                     5
aat gag agg atc cag gag gtc gcc ggc tcc cta ata ttt agg gca ata
                                                                  205
Asn Glu Arg Ile Gln Glu Val Ala Gly Ser Leu Ile Phe Arg Ala Ile
               15
                                  20
age age att gge ega ggg age gag age gte ace tee agg ggg gae etg
                                                                  253
Ser Ser Ile Gly Arg Gly Ser Glu Ser Val Thr Ser Arg Gly Asp Leu
           30
get act tge eec ega gge tte gee gte ace gge tge act tgt gge tee
                                                                  301
Ala Thr Cys Pro Arg Gly Phe Ala Val Thr Gly Cys Thr Cys Gly Ser
       45
                          50
gcc tgt ggc tcg tgg gat gtg cgc gcc gag acc aca tgt cac tgc cag
                                                                  349
Ala Cys Gly Ser Trp Asp Val Arg Ala Glu Thr Thr Cys His Cys Gln
                      65
                                          70
tgc gcg ggc atg gac tgg acc gga gcg cgc tgc tgt cgt gtg cag ccc
                                                                  397
Cys Ala Gly Met Asp Trp Thr Gly Ala Arg Cys Cys Arg Val Gln Pro
                   80
                                      85
tgaggtcgcg cgcagcgcgt gcacagcgcg ggcggaggcg gctccaggtc cggaggggtt
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517
                                                                  518
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<223> Von Heijne matrix
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score 6.5
seq SCLCPALFPGTSS/FI

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<221> polyA_site <222> 339..350

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acgtcattcc aaaaccacac ccttgcaaag ctttgtactc cgcaccccag atg atc 56 tcc agg cag ctc aga tct ctt tcc tgc ctt tgc cct gca ctg ttc ccc Ser Arg Gln Leu Arg Ser Leu Ser Cys Leu Cys Pro Ala Leu Phe Pro -15 -10 ggt act tcc tcc ttt att gta gca ctc agc tcc cca gcc gat ctg tac 152 Gly Thr Ser Ser Phe Ile Val Ala Leu Ser Ser Pro Ala Asp Leu Tyr atc cct cav agg cas cga tct gat gaa ttg gtt ttt gaa tcc car aaa 200 Ile Pro Xaa Arg Xaa Arg Ser Asp Glu Leu Val Phe Glu Ser Gln Lys 20 ggg tot gcc atg gag ttg gca gtc atc acg gta rat ggc gta 242 Gly Ser Ala Met Glu Leu Ala Val Ile Thr Val Xaa Gly Val 35 40 tgattttgct gaattttaaa taaaatgaaa accataaatt acatratgct tttattgach 302 cttgacmact ggcctaaata aaaaractct gactccaaaa aaaaaaaa 350

<210> 249

<211> 996

<212> DNA

<213> Homo sapiens

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<222> 111..191

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 score 5.80000019073486
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<221> polyA_signal

<222> 965..970

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<222> 986..996

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cagcaatgct cagctcataa tgatgtcaag caccatggcc agttttatga atg ggy

Met Gly

-15

ttc ctg wgt cta atg acc ctg aca acc cat gtt cac tca agt gcc aag

Phe Leu Xaa Leu Met Thr Leu Thr Thr His Val His Ser Ser Ala Lys

-10

-5

1

cca aat gaa caa ccc tgg ttg ttg aac tagcacctaa ggtcttarat

Pro Asn Glu Gln Pro Trp Leu Leu Asn

5

10

164

211

ggtacgcgtt gctatacaga atctttggat atgtgcatca gtggtttatg ccaaattgtt 271

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331

391

451

ggctgcgatc accagctggg aagcaccgtc aaggaarata actgtggggt ctgcaacrga

natgggtcca cctgccggct ggtccgaggg cartataaat cccakctctc cgcaaccaaa

tergatgata etgtggttge aatteeetat ggaagtakae atattegeet tgtettaaaa

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ggtcctgatc acttatatct ggaarccawa accctccagg ggactaawgg tgaaaacagt
                                                                      511
ctcasctcca caggaacttt ccttgtggac aattctagtg tggacttcca gaawtttcca
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gacwdagaga tactgagaat ggctggacca ctcacagcag atttcattgt caawattcgt
aactcgggct ccgctgacag tacagtccag kkcatcttct atcaacccat catccaccga
tggagggara cggatttctt tccttgctca gcaacctgtg gaggaggtta tcagctgaca
                                                                      751
teggetgagt getacgatet gaggageaac egtgtggttg etgaceaata etgteaetat
                                                                      811
tacccagaga acatcaaacc caaacccaag cttcaggagt gcaacttgga tccttgtcca
                                                                      871
gccaggtcag tcaaatttgc tagttcattt gtcataaaca taactcaagt tccaaatagg
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ttatttaaat taaaatgaaa cgttttaatt aaaaataaaa tgaaattaaa catcaaaaaa
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aaaaa
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                                                                      56
                                                 Met Ser Pro Ser
ggt cgc ctg tgt ctt ctc acc atc gtt ggc ctg att ctc ccc acc aga
                                                                     104
Gly Arg Leu Cys Leu Leu Thr Ile Val Gly Leu Ile Leu Pro Thr Arg
        -15
                            -10
                                                -5
gga cag acg ttg aaa gat acc acg tcc agt tct tca gca gac tca act
                                                                     152
Gly Gln Thr Leu Lys Asp Thr Thr Ser Ser Ser Ser Ala Asp Ser Thr
                                        10
atc atg gac att cag gtc ccg aca cga gcc cca gat gca gtc tac aca
                                                                     200
Ile Met Asp Ile Gln Val Pro Thr Arg Ala Pro Asp Ala Val Tyr Thr
               20
                                    25
gaa ctc cag ccc acc tct cca acc cca acc tgg cct gct gat gaa aca
                                                                     248
Glu Leu Gln Pro Thr Ser Pro Thr Pro Thr Trp Pro Ala Asp Glu Thr
                                40
                                                    45
cca caa ccc cag acc cag caa ctg gaa gga acg gat ggg cct
                                                                     296
Pro Gln Pro Gln Thr Gln Gln Leu Glu Gly Thr Asp Gly Pro
                            55
cta gtg aca gat cca gag aca cac wak agc mcc aaa gca gct cat ccc
                                                                     344
Leu Val Thr Asp Pro Glu Thr His Xaa Ser Xaa Lys Ala Ala His Pro
                        70
act gat gac acc acg acg ctc tct gag aga cca tcc cca agc aca kac
                                                                     392
Thr Asp Asp Thr Thr Leu Ser Glu Arg Pro Ser Pro Ser Thr Xaa
                    85
                                        90
                                                            95
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gtc cat dad Val His Xaa	aga ccb Arg Pro 100	cba kda Xaa Xaa	ccc tca Pro Ser	akc cat Xaa His 105	ctg gtt Leu Val	ttc atg Phe Met 110	agg Arg	44 0
atg acc cct Met Thr Pro	tct tct	atg atg Met Met	aac aca Asn Thr 120	ccc tcc	gga aac Gly Asn	sgg ggc	tgt (488
tgg tcg cag Trp Ser Glr	ı Leu Cys	tgt tca Cys Ser	tca cag	gca tca Ala Ser	tca tcc Ser Ser 140	tca cca	gtg ! Val	536
gca agt gca Ala Ser Ala 145	a ggc agc a Gly Ser	tgt ccc Cys Pro 150	ggt tat	gcc gga Ala Gly	atc att	gca ggt Ala Gly	gag ! Glu	584
tcc atc aga Ser Ile Arc 160			aacctg (ctgggcac		caag	e	632
ccccctgcca ggaagacaca aaccctgccc tctgctaaga	gatgatga: gccctga:	tg cccago ag ctggag ag gctaco	ccag ggo	ctgccggt cttggggg	ccgagtct	cc tacct	cccc 7	692 752 812 860
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ctt ctc ccg Leu Leu Pro	ttg ctg Leu Leu	ctg ctg (Leu Leu 1	-25 ctc tgc	ggc cct	tcc cag g Ser Gln A) Tat caa t	:qc 1	01
cga cct gta Arg Pro Val	ctc cag Leu Gln 5	-10 aat ctg t Asn Leu I	Leu Gln	agc cca Ser Pro 10	-5 ggc ttg a Gly Leu 1	aca tgg a Thr Trp S	igc 1	49
ttg gaa gtg Leu Glu Val	ccc act	ggg aga g Gly Arg (gaa gga	aaq qaa	Gly Gly A	at cgg d	gga 1 Sly	97
cca ggg cta Pro Gly Leu 35	Xaa Gly	Ala Thr I	cca gcc Pro Ala .	Arg Ser	cct cag of Pro Gln 0	ggc aag g Sly Lys G	lu	45
atg ggg aga Met Gly Arg 50	caa agg Gln Arg	acc aga a Thr Arg I 55	aag gtg Lys Val	aag ggc Lys Gly	cct act t	gg akt o Trp Xaa H	ac 2	93

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aca gca aat cag gaa cta aac agg atg agg tct ctg tct tct ggc tcc Thr Ala Asn Gln Glu Leu Asn Arg Met Arg Ser Leu Ser Ser Gly Ser 65 70 75 80	341
gtg cca gtg ggg cat ctg gag ggt ggc acg gtc aag ctt cag aag gac Val Pro Val Gly His Leu Glu Gly Gly Thr Val Lys Leu Gln Lys Asp	389
85 90 95	437
acg ggc ctc cat tcc tgc ara gat ggt atg gct tct ctt gaa ggg acg Thr Gly Leu His Ser Cys Xaa Asp Gly Met Ala Ser Leu Glu Gly Thr 100 105 110	437
cca gct tca gtc ctg gct gat gct tgc cca gga ttc cat gat gtg aan	485
Pro Ala Ser Val Leu Ala Asp Ala Cys Pro Gly Phe His Asp Val Xaa 115 120 125	
gtt car arg gcc cta ttt ggg tta agt ggg ana rta ctg tgg ctg aaa	533
Val Gln Xaa Ala Leu Phe Gly Leu Ser Gly Xaa Xaa Leu Trp Leu Lys 130 135 140	
acc cac ttc tgc ctt tct att ana ctt taaataaact ctgaaracct	580
Thr His Phe Cys Leu Ser Ile Xaa Leu 145 150	
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seq VAFMLTLPILVCK/VQ	
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Met Ala Thr	
aca gtc cct gat ggt tgc cgc aat ggc ctg aaa tcc aag tac tac aga Thr Val Pro Asp Gly Cys Arg Asn Gly Leu Lys Ser Lys Tyr Tyr Arg	165
-50 -45 -40	
ctt tgt gat aag gct gaa gct tgg ggc atc gtc cta gaa acg gtg gcc	213
Leu Cys Asp Lys Ala Glu Ala Trp Gly Ile Val Leu Glu Thr Val Ala -35 -25	
aca gcc ggg gtt gtg acc tcg gtg gcc ttc atg ctg act ctc ccg atc	261
Thr Ala Gly Val Val Thr Ser Val Ala Phe Met Leu Thr Leu Pro Ile -20 -15 -10 -5	
	309
ctc gtc tgc aag gtg cag gac tcc aac agg cga aaa atg ctg cct act	
Leu Val Cys Lys Val Gln Asp Ser Asn Arg Arg Lys Met Leu Pro Thr	
	357
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Leu Val Cys Lys Val Gln Asp Ser Asn Arg Arg Lys Met Leu Pro Thr 1 5 10 cag ttt ctc ttc ctc ctg ggt gtg ttg ggc atc ttt ggc ctc acc ttc Gln Phe Leu Phe Leu Gly Val Leu Gly Ile Phe Gly Leu Thr Phe 15 20 25	357 405
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atc tcc atc ttc cct act atg atg gtg tgt atg atg gcc tgg cga ccc
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Ile Ser Ile Phe Pro Thr Met Met Val Cys Met Met Ala Trp Arg Pro
                                        -50
                    -55
att cag gca ctt atg gcc att tca gcc act ttc aag atg tta gaa agt
                                                                      148
Ile Gln Ala Leu Met Ala Ile Ser Ala Thr Phe Lys Met Leu Glu Ser
                                    -35
                -40
tca agc cag aag ttt ctt cag ggt ttg gtc tat ctc att ggg aac ctg
                                                                      196
Ser Ser Gln Lys Phe Leu Gln Gly Leu Val Tyr Leu Ile Gly Asn Leu
           -25
                                -20
atg ggt ttg gca ttg gct gtt tac aag tgc cag tcc atg gga ctg tta
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Met Gly Leu Ala Leu Ala Val Tyr Lys Cys Gln Ser Met Gly Leu Leu
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cct aca cat gca tcg gat tgg tta gcc ttc att gag ccc cct gag aga
Pro Thr His Ala Ser Asp Trp Leu Ala Phe Ile Glu Pro Pro Glu Arg
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atg gag tca gtg gtg gag gac tgc ttt tgt gaa cat gag aaa gca gcg
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Met Glu Ser Val Val Glu Asp Cys Phe Cys Glu His Glu Lys Ala Ala
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cct ggt ccc tat gta ttt ggg tct tat tta cat cct tct tta agc cca
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Pro Gly Pro Tyr Val Phe Gly Ser Tyr Leu His Pro Ser Leu Ser Pro
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gtg gct cct cag cat act ctt aaa cta atc act tat gtt aaa aaa aac
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Val Ala Pro Gln His Thr Leu Lys Leu Ile Thr Tyr Val Lys Lys Asn
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cgctgccctc ctgcctgcag cc atg acg ccc ctg ctc acc ctg atc ctg gtg
                                                                      292
                         Met Thr Pro Leu Leu Thr Leu Ile Leu Val
                         -20
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Val Leu Met Gly Leu Pro Leu Ala Gln Ala Leu Asp Cys His Val Cys
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                                                                      388
ged tad aad gga gad aad tgd ttd aad ddd atg dgd tgd deg get atg
Ala Tyr Asn Gly Asp Asn Cys Phe Asn Pro Met Arg Cys Pro Ala Met
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gtt gcc tac tgc atg acc acg cgc acc tac tac acc ccc acc agg atg
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Val Ala Tyr Cys Met Thr Thr Arg Thr Tyr Tyr Thr Pro Thr Arg Met
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                                                                      481
aaq qtc aqt aaq tcc tqc qtg ccc cgc tgc ttc gar nac tgt gta
Lys Val Ser Lys Ser Cys Val Pro Arg Cys Phe Glu Xaa Cys Val
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getayaccet ckcacceake teaccetgee teacceteca cactecetge gaccteetea
                                                                      721
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Cys Gly Ser Leu Leu Pro Gly Leu Trp Gln His Leu Thr Ala Asn His

-5

-10

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tcc ctg aac caa gag cca ttc gty tca aga gcc att cgt cca aag tac Ser Leu Asn Gln Glu Pro Phe Val Ser Arg Ala Ile Arg Pro Lys Tyr 40 45 50	422
tot atc acc tagccattgt akccatacca agccgggctt cctacttccc Ser Ile Thr 55	471
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440

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ttc atc ggc att gga gaa att tta ggt gga agc ctc ttc ggc ctg Phe Ile Gly Ile Gly Glu Ile Leu Gly Gly Ser Leu Phe Gly Leu Leu 20 25 30	194
age aag aac aat egt ttt ggt aga aat eea gtt gtg etg ttg gge ate	242
Ser Lys Asn Asn Arg Phe Gly Arg Asn Pro Val Val Leu Leu Gly Ile	
Ser Lys Asn Asn Arg Phe Gly Arg Asn Pro Val Val Leu Leu Gly Ile	290
Ser Lys Asn Asn Arg Phe Gly Arg Asn Pro Val Val Leu Leu Gly Ile 35 40 45 50 ctg gtg cac ttc ata gct ttt tat cta ata ttt ctc aac atg cct gga Leu Val His Phe Ile Ala Phe Tyr Leu Ile Phe Leu Asn Met Pro Gly	290 338

0.5	
85 90 95 gga aac agc tgc ttt aat acc cas ctg ctt akt atc tkg ggc ttt ctg	434
Gly Asn Ser Cys Phe Asn Thr Xaa Leu Leu Xaa Ile Xaa Gly Phe Leu 100 105 110	
tat tot gaa rac ago goo coa koa ttt goo ato tto aat ttt gtt cag	482
Tyr Ser Glu Xaa Ser Ala Pro Xaa Phe Ala Ile Phe Asn Phe Val Gln	
115 120 125 130	
tot att tgc gca gcc gtg gca ttt ttc tac agc aac tac ctt ctc ctt	530
Ser Ile Cys Ala Ala Val Ala Phe Phe Tyr Ser Asn Tyr Leu Leu Leu	
135 140 145	
cac tgg caa ctc ctg gtc atg gtk atw ttt ggg ttt ttk gga aca att	578
His Trp Gln Leu Leu Val Met Val Ile Phe Gly Phe Xaa Gly Thr Ile 150 155 160	
tot the the act greg gaa tog gaa set god god the gra see ege gge	626
Ser Phe Phe Thr Val Glu Trp Glu Xaa Ala Ala Phe Val Xaa Arg Gly	
165 170 175	
tot gao tac cga agt ato tgatotggtg toogtgaggg gacacgtatg	674
Ser Asp Tyr Arg Ser Ile 180	
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Asn Lys Ser Tyr Lys Asn Lys Asp Ser Val Arg Ile Tyr Leu Ser Leu -70 -65 -60	
tgc aca gtg agc att aaa ttt aca tac ttt cat gat ata cag act aat	210
Cys Thr Val Ser Ile Lys Phe Thr Tyr Phe His Asp Ile Gln Thr Asn	
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-40 -35 -30 -25	
ggt ggt too att tta cag cac toa gtg gat coc ctt gtt ttg tto cta	306
Gly Gly Ser Ile Leu Gln His Ser Val Asp Pro Leu Val Leu Phe Leu	300
GIA GIA SET THE TER GILL UIR SET AND WED NIO TER AND THE THE THE	

-20 -15 -10	
ago otg goo otg tta gtg aca oco act too aco oct tot got aar ata.	354.
Ser Leu Ala Leu Leu Val Thr Pro Thr Ser Thr Pro Ser Ala Lys Ile	
-5 1 5	
car ago ott caa att gac otc oot gga ggo tgg agg otg goo act gac	402
Gln Ser Leu Gln Ile Asp Leu Pro Gly Gly Trp Arg Leu Ala Thr Asp	
10 15 20	
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Arg Ile Phe Thr Leu Ser Pro Val Pro Met Asp Xaa Pro Leu Ile Leu	
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His Gln Leu	
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Met Glu Lys Ser Trp Met Leu Trp Asn Phe Val Glu Arg Trp	
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Leu Ile Ala Leu Ala Ser Trp Ser Trp Ala Leu Cys Arg Ile Ser Leu	
-10 -5 1	
tta cct tta ata gtg act ttt cat ctg tat gga ggc att atc tta ctt	207
Leu Pro Leu Ile Val Thr Phe His Leu Tyr Gly Gly Ile Ile Leu Leu	
5 10 15 20	
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Val Leu Leu Tyr Phe Pro Xaa Gln Xaa Ser Ser Ser Arg Leu Tyr Asp
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Ser His Ala His Trp Xaa Ser Xaa
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Gln Arg Ala Leu Ser His Pro Ala Pro Phe Leu Thr Xaa Xaa Lys Asn
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Pro Phe Leu Trp Lys Leu
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Leu Xaa Gln Ala Ser Pro Ser Pro His Pro His Arg Xaa Arg Ile Trp	
15 20 25	434
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-35
                    -30
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Thr Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp
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Leu Trp Ser Thr Tyr Gln Val Arg Xaa Ala Asp Trp Ser Leu Glu Ala
                                     55
 tta ctc tac aaa tgg gat atg aaa tgt gtc cac att cct ctt gag tct
                                                                       539
Leu Leu Tyr Lys Trp Asp Met Lys Cys Val His Ile Pro Leu Glu Ser
                                 70
 ttt gat gca gac aaa gaa rat ata gca gaa tct acc ctt cca gga aga
                                                                       587
 Phe Asp Ala Asp Lys Glu Xaa Ile Ala Glu Ser Thr Leu Pro Gly Arg
                             85
        80
 cat aca gtt gaa atg ctg gtc att tcc ttt gca aag gac agt ctc
                                                                       632
 His Thr Val Glu Met Leu Val Ile Ser Phe Ala Lys Asp Ser Leu
                                             105
 tgaattatac ctacaacctg ttctgggaca gtatcaatac tgatgagcaa cctggcacac
                                                                       692
 aaactatgag cagaccactt cagcttgaga atgcagtggg tctgaagatg gtcaagtctg
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                     Met Thr Ser Gly Gln Ala Arg Ala Ser Xaa Gln
                                  -105
tcc ccc cag gcc ctg gag gac tcg ggc ccg gtg aat atc tca gtc tca
                                                                      101
Ser Pro Gln Ala Leu Glu Asp Ser Gly Pro Val Asn Ile Ser Val Ser
        -95
                            -90
                                                -85
atc acc cta acc ctg gac cca ctg aaa ccc ttc.gga ggg tat tcc cgc
                                                                      149
Ile Thr Leu Thr Leu Asp Pro Leu Lys Pro Phe Gly Gly Tyr Ser Arg
                       -75
                                          -70
aac gtc acc cat ctg tac tca acc atc tta ggg cat cag att gga ctt
                                                                      197
Asn Val Thr His Leu Tyr Ser Thr Ile Leu Gly His Gln Ile Gly Leu
                   -60
                                        -55
tca ggc agg gaa gcc cac gag gag ata aac atc acc ttc acc ctg cct
                                                                      245
Ser Gly Arg Glu Ala His Glu Glu Ile Asn Ile Thr Phe Thr Leu Pro
                -45
                                    -40
aca gcg tgg agc tca gat gac tgc gcc ctc cac ggt cac tgt gag cag
                                                                      293
Thr Ala Trp Ser Ser Asp Asp Cys Ala Leu His Gly His Cys Glu Gln
            -30
                                -25
                                                    -20
gtg gta ttc aca gcc tgc atg acc ctc acg gcc agc cct ggg gtg ttc
                                                                      341
Val Val Phe Thr Ala Cys Met Thr Leu Thr Ala Ser Pro Gly Val Phe
        -15
                            -10
                                                -5.
ccg tca ctg tac agc cac cgc act gtg ttc ctg aca cgt aca gca acg
                                                                      389
Pro Ser Leu Tyr Ser His Arg Thr Val Phe Leu Thr Arg Thr Ala Thr
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cca cgc tct ggt aca aga tct tca caa ctg cca gag atg cca aca caa
                                                                      437
Pro Arg Ser Gly Thr Arg Ser Ser Gln Leu Pro Glu Met Pro Thr Gln
                                    25
aat acg ccc aaa att aca atc ctt tct ggt gtt ata agg ggg cca ttg
                                                                      485
Asn Thr Pro Lys Ile Thr Ile Leu Ser Gly Val Ile Arg Gly Pro Leu
                                40
gaa aag tot ato atg ott taaatoocaa gottacagtg attgttocag
                                                                      533
Glu Lys Ser Ile Met Leu
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atgatgaccg ttcattaata aatttgcatc tcatgcacac cagttacttc ctctttgtga
                                                                      593
tggtgataac aatgttttgc tatgctgtta tcaagggcag acctagcaaa ttgcgtcaga
                                                                      653
gcaatcctga attttgtccc gagaaggtgg ctttggctga agcctaattc cacagctcct
                                                                      713
tgttttttga gagagactga gagaaccata atccttgcct gctgaaccca gcctgggcct
                                                                      773
ggatgctctg tgaatacatt atcttgcgat gttgggttat tccagccaaa gacatttcaa
                                                                      833
gtgcctgtaa ctgatttgta catatttata aaaatctatt cagaaattgg tccaataatg
                                                                      893
cacqtgcttt gccctgggta cagccagagc ccttcaaccc caccttggac ttgaggacct
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1013

1073

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                                                                  1133
ttgcatttcc aaagccacca atccattttg tggattttat gtgtctgtgg cttaataatc
                                                                  1193
atagtaacaa caataatacc tttttctcca ttttgcttgc aggaaacata ccttaagttt
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Met Leu Gly Gly Asp His Arg Ala Leu Leu Leu Lys Ile Trp Leu Leu
                       -15
                                          -10
caa agg cca gag tca cag gaa gga ctt ctt cca ggg aga tta gtg gtg
                                                                    96
Gln Arg Pro Glu Ser Gln Glu Gly Leu Leu Pro Gly Arg Leu Val Val
- 5
                   1
atg gag agg aga gtt aaa aat gac ctc atg tcc ttc ttg tcc acg gtt
                                                                   144
Met Glu Arg Arg Val Lys Asn Asp Leu Met Ser Phe Leu Ser Thr Val
                               20
ttg ttg agt ttt cac tct tct aat gca agg gtc tca cac tgt gaa cca
                                                                   192
Leu Leu Ser Phe His Ser Ser Asn Ala Arg Val Ser His Cys Glu Pro
       30
ctt agg atg tgatcacttt caggtggcca ggaatgttga atgtctttgg
                                                                   241
Leu Arg Met
   45
ctcagttcat ttaaaaaaga tatctatttg aaagttctca rarttgtaca tatgtttcac
                                                                   301
agtacaggat ctgtacataa aagtttcttt cctaaaccat tcaccaagag ccaatatcta
                                                                   361
ggcattttct tggtagcaca aattttctta ttgcttaraa aattgtcctc cttgttattt
                                                                   421
ctgtttgtaa racttaagtg agttaggtct ttaaggaaag caacgctcct ctgaaatgct
tgtctttttt ctgttgccga aatarctggt cctttttcgg gagttaratg tatarartgt
ttgtatgtaa acatttcttg taggcatcac catgaacaaa gatatatttt ctatttattt
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aaaaaaaaa
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<222> 1587..1597
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                                          Met Ile Xaa Leu Arg Asp
                                                  -30
aca get gee tee ete ege ett gag aga gae aca agg eag ttg eea etg
                                                                      104
Thr Ala Ala Ser Leu Arg Leu Glu Arg Asp Thr Arg Gln Leu Pro Leu
                        -20
                                            -15
ctc acc agt gcc ctg cac gga ctg cag cag cag cac cca gcc ttc tct
                                                                      152
Leu Thr Ser Ala Leu His Gly Leu Gln Gln His Pro Ala Phe Ser
                    - 5
                                                                      200
ggt gtg gca cgg ctg gcc aag cgg tgg gtg cgt gcc cag ctt ctt ggt
Gly Val Ala Arg Leu Ala Lys Arg Trp Val Arg Ala Gln Leu Leu Gly
                                15
gag ggt ttc gct gat gag agc ctg gat ctg gtg gcc gct gcc ctt ttc
                                                                      248
Glu Gly Phe Ala Asp Glu Ser Leu Asp Leu Val Ala Ala Ala Leu Phe
                            30
                                                                      296
ctg cac cct gag ccc ttc acc cct ccg agt tcc ccc cag gtt ggc ttc
Leu His Pro Glu Pro Phe Thr Pro Pro Ser Ser Pro Gln Val Gly Phe
                       45
ctt cga ttc ctt ttc ttg gta tca acg ttt gat tgg aag aac aac ccc
                                                                      344
Leu Arg Phe Leu Phe Leu Val Ser Thr Phe Asp Trp Lys Asn Asn Pro
                   60
                                        65
ctc ttt gtc aac ctc aat aat gag ctc act gtg gag gag cag gtg gar
                                                                      392
Leu Phe Val Asn Leu Asn Asn Glu Leu Thr Val Glu Glu Gln Val Glu
               75
                                    80
ate ege agt gge tte etg gea get egg gea eag ete eee gte atg gte
                                                                      440
Ile Arg Ser Gly Phe Leu Ala Ala Arg Ala Gln Leu Pro Val Met Val
                                95
            90
att gtt acc ccc caa rac cgc aaa aac tct gtg tgg aca cag gat gga
                                                                      488
Ile Val Thr Pro Gln Xaa Arg Lys Asn Ser Val Trp Thr Gln Asp Gly
                            110
ccc tca gcc car atc ctg cag cag ctt gtg gtc ctg gca gct gaa scc
                                                                      536
Pro Ser Ala Gln Ile Leu Gln Gln Leu Val Val Leu Ala Ala Glu Xaa
                        125
ctg ccc atg tta rar aas cag ctc atg gat ccc cgg gga cct ggg gac
                                                                      584
Leu Pro Met Leu Xaa Xaa Gln Leu Met Asp Pro Arg Gly Pro Gly Asp
135
                    140
                                        145
atc agg aca gkg ttc cgg ccg ccc ttg gac att tac gac gtg ctg att
                                                                      632
Ile Arg Thr Xaa Phe Arg Pro Pro Leu Asp Ile Tyr Asp Val Leu Ile
                                    160
ege etg tet eet ege cat ate eeg egg cae ege eag get gtg gae ter
                                                                      680
Arg Leu Ser Pro Arg His Ile Pro Arg His Arg Gln Ala Val Asp Ser
            170
                                175
cca get gee tee tte tge egg gge etg ete age eag eeg ggg eee tea
                                                                      728
Pro Ala Ala Ser Phe Cys Arg Gly Leu Leu Ser Gln Pro Gly Pro Ser
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185 190 195	
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Ser Leu Met Pro Val Leu Gly Xaa Asp Pro Pro Gln Leu Tyr Leu Thr	
200 205 210	
cag ctc arg gag gcc ttt ggg gat ctg gcc ctt ttc ttc tat gac cag	824
Gln Leu Xaa Glu Ala Phe Gly Asp Leu Ala Leu Phe Phe Tyr Asp Gln	
215 220 225 230	
cat ggt gga gag gtg att ggt gtc ctc tgg aag ccc acc agc ttc cag	872
His Gly Gly Glu Val Ile Gly Val Leu Trp Lys Pro Thr Ser Phe Gln	
235 240 245	
ccg cag ccc ttc aag gcc tcc agc aca aag ggg cgc atg gtg atg tct	920
Pro Gln Pro Phe Lys Ala Ser Ser Thr Lys Gly Arg Met Val Met Ser	
250 255 260	
cga ggt ggg gag cta gta atg gtg ccc aat gtt gaa gca atc ctg gag	968
Arg Gly Glu Leu Val Met Val Pro Asn Val Glu Ala Ile Leu Glu	
265 270 275	
gac ttt gct gtg ctg ggt gaa ggc ctg gtg cag act gtg gag gcc cga	1016
Asp Phe Ala Val Leu Gly Glu Gly Leu Val Gln Thr Val Glu Ala Arg	
280 285 290	
agt gag agg tgg act gtg tgatcccagc tctggagcaa gctgtagacg	1064
Ser Glu Arg Trp Thr Val	
295 300	
gacagcagga cattggacct ctagagcaag atgtcagtag gatgacctcc accctccttg	1124
gacatgaatc ctccatggag ggcctgctgg ctgaacatgc tgaatcatct ccaacaaaac	1184
ccagccccaa ctttctctct gatgctccag cattggggca ggggcatggt ggcccatgta	1244
gteteetggg ceteaceate ceagaagagg agtgggagee ageteagaga aggaactgaa	1304
cccaggagat ccatccacct attagccctg ggcctggacc tccctgcgat ttcccactcc	1364
tttcttagtc ttcttccaga aacagagaag gggatgtgtg cetgggagag gctctgtctc	1424
cttcctgctg ccaggacctg tgcctagact tagcatgccc ttcactgcag tgtcaggcct	1484
ttagatggga cccagcgaaa atgtggccct tctgagtcac atcaccgaca ctgagcagtg	1544
gaaaggggct atatgtgtat gaatagacca cattgaagga gcaaaaaaaa aaamcch	1601

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Met Gly Gly Ile Trp Asn Ala Leu Ser Met Ser Ser Phe Ser
-15
-10
ttt cat tca tcc tcc tgc tca gca ctg tca gcc aag agc tta ctc agc
Phe His Ser Ser Ser Cys Ser Ala Leu Ser Ala Lys Ser Leu Leu Ser

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- 5
                    1
                                    5
aga cac cac ata ctg cag cag ttc cta gtg aga aaa tct gtg cca cta 🕟
                                                                      206 .
Arg His His Ile Leu Gln Gln Phe Leu Val Arg Lys Ser Val Pro Leu
            15
                                20
                                                    25
gaa aat gct tca ctt cca ttt cct cac ctg ggc agt tct ctg ttt aaa
                                                                      254
Glu Asn Ala Ser Leu Pro Phe Pro His Leu Gly Ser Ser Leu Phe Lys
                            35
att gtg ggc tgatttggtc ttcctctcct cctcccactg ttactgccct.
                                                                      303
Ile Val Gly
    45
gcagcccttg ttcaggtgta cagaccctta ttctggcctc tagtgtcctt gtctgtcatg
                                                                      363
acacaccett cegeceaaat acetetgace ceaaggetgg aatggggetg gtaggarata
                                                                      423
agtttgctta ctcatartca tgtcctttct cttggcacct gcttccctgc ggtgtcctca
                                                                      483
aatggatttc tgtgtggcag tggartgatt gcatgaattt ttctgtaaca cattaacttt
                                                                      543
gtattattat taagggartt tgaraaagct ttgcttataa tgtcaaggca aggaggtaaa
                                                                      603
aactggagcc caaakaaatt cccttagggc aagattatgt tataataraa aattgaattt
                                                                      663
cctgaggcag tggctgccac cccttttcar atgtttagtc ctgcaaatag catctttctt
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gtagtctgtg acatggatgg ggatgctagg gcccttaggg gcaaggggac taaactaaat
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caakttgagt ttttttccag caggggttar gggaggtact csctgttgat atttgacact
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araaagtaat cttttttaca aaactgtttt tctaggtggg tggaaagtga aactgccaca
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teettgttgg tttagteeaa rarateattt geaacaacag taratgteeg ggttttgttt
                                                                      963
ctgtcttttt attatgaaaa actatgttaa gggggaaaat gtggattatg gtaaccarag
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gaatccctas ccttgttttc cttaraarac ttgtttagtg ttttatcara cgtctgttgt
                                                                     1083
agttgtarac aggaaagctt gtgaraaaaa caccacatgg ascctgtaaa tgtttttgca
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tgcctgagga ggcctcggtt ggatgcgaag gagctgcagc atccagggga caag atg
                                                                       117
                                                             Met
cca act ggc aag cag cta gct gac att ggc tat aag acc ttc tct acc
                                                                       165
Pro Thr Gly Lys Gln Leu Ala Asp Ile Gly Tyr Lys Thr Phe Ser Thr
                -25
                                    -20
                                                         -15
tcc atg atg ctt ctc act gtg tat ggg ggg tac ctc tgc agt gtc cga
                                                                       213
Ser Met Met Leu Leu Thr Val Tyr Gly Gly Tyr Leu Cys Ser Val Arg
            -10
                                -5
gtc tac cac tat ttc cag tgg cgc agg gcc cag cgc cag gcc gca gaa
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261

Val Tyr His Tyr Phe Gln Trp Arg Arg Ala Gln Arg Gln Ala Ala Glu 5 10 15	
gaa cag aag dac tca gga atc atg tagaactggg gggctttttc tcctgagcar Glu Gln Lys Xaa Ser Gly Ile Met 20 25	315
asakgcccaa ggcatgctgt ggagagactt cacctgccac catttccagg tcaacaggac	375
tagagegttg atggttttca aaccetgttg gaagaaagtg cecatggttt etetggttet	435
gccartttga cagtttatgg argcttttga atcgtaatar caatgtgagg gtgargtaca	495 536
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seg LLLITAILAVAVG/FP	
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201. malan ada	
<221> polyA_site <222> 515527	
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-15 -10	
aca gcc atc ttg gca gtg gct gtw ggt ttc cca gtc tct caa gac cag	161
Thr Ala Ile Leu Ala Val Ala Val Gly Phe Pro Val Ser Gln Asp Gln -5 1 5	
gaa cga gaa aaa aga agt atc agt gac agc gat gaa tta gct tca ggr	209
Glu Arg Glu Lys Arg Ser Ile Ser Asp Ser Asp Glu Leu Ala Ser Gly	
10 15 20	
with tit gig the ect tac eca tat eca tit ege eca ett eca eca att	257
Xaa Phe Val Phe Pro Tyr Pro Tyr Pro Phe Arg Pro Leu Pro Pro Ile 25 30 35	
cca ttt cca aga ttt cca tgg ttt aga cgt aat ttt cct att cca ata	305
Pro Phe Pro Arg Phe Pro Trp Phe Arg Arg Asn Phe Pro Ile Pro Ile	
40	3.5.4
cct gaa tct gcc cct aca act ccc ctt cct agc gaa aag taaacaaraa Pro Glu Ser Ala Pro Thr Thr Pro Leu Pro Ser Glu Lys	354
60 65	
ggaaaagtca crataaacct ggtcacctga aattgaaatt gagccacttc cttgaaraat	414
caaaattcct gttaataaaa raaaaacaaa tgtaattgaa atagcacaca gcattctcta	474
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                                                                      59
                                                              Met
aag aaa gtt ctc ctc ctg atc aca gcc atc ttg gca gtg gct gtt ggt
                                                                     107
Lys Lys Val Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val Gly
    -15
                        -10
ttc cca gtc tct caa gac cak gaa cga gaa aaa aga agt atc agt gac
                                                                     155
Phe Pro Val Ser Gln Asp Xaa Glu Arg Glu Lys Arg Ser Ile Ser Asp
                                    10
               5
age gat gaa tta get tea ggg ttt ttt gtg tte eet tae eea tat eea
                                                                     203
Ser Asp Glu Leu Ala Ser Gly Phe Phe Val Phe Pro Tyr Pro Tyr Pro
                                25
ttt cgc cca ctt cca cca att cca ttt cca aga ttt cca tgg ttt aga
                                                                     251
Phe Arg Pro Leu Pro Pro Ile Pro Phe Pro Arg Phe Pro Trp Phe Arg
                            40
                                                                     299
egt aat tit eet att eea ata eet gaa tet gee eet aca aet eee ett
Arg Asn Phe Pro Ile Pro Ile Pro Glu Ser Ala Pro Thr Thr Pro Leu
                       55
                                            60
ccg agc gaa aag taaacaagaa ggaaaagtca cgataaacct ggtcacctga
                                                                     351
Pro Ser Glu Lys
aattgaaatt gagccacttc cttgargaat caaaattcct gttaataaaa gaaaaacaaa
                                                                     411
tgtaattgaa atagcacaca gcattctcta gtcaatatct ttagtgatct tctttaataa
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acatgaaagc aaaaaaaaa aa
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tgc agc tac gct acc agg aga tct cca agc gaa ctc agc ctc ctc cca	61
Cys Ser Tyr Ala Thr Arg Arg Ser Pro Ser Glu Leu Ser Leu Leu Pro	
-20 -15 -10	Λ.
age tee etg tgg gte eta gee aca age tet eca aca att act att gea 20 Ser Ser Leu Trp Val Leu Ala Thr Ser Ser Pro Thr Ile Thr Ile Ala	09
-5 1 5	
3-3 3 3 3	57
Leu Ala Met Ala Ala Gly Asn Leu Cys Pro Leu Pro Ser Ser Xaa Arg	
10 15 20 25 crc aaa agg cgc tgg tgt cag gca asc car caa ara gct ctg ctg 30	02
Xaa Lys Arg Arg Trp Cys Gln Ala Xaa Gln Gln Xaa Ala Leu Leu	-
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3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3	71
Leu Pro Thr His Asp Pro Pro Thr Pro Ala His Trp Ser Pro Ala Ser -35 -20 -20	
	19
His Gln Gln Phe Lys His Xaa Ser Pro Leu Leu Thr Leu Ala Leu Leu	
-15 -10 -5	
ggt cag tgc tct ctg ttc arc aat ttg agg aaa aaa ctt gca ggg caa 36 Gly Gln Cys Ser Leu Phe Xaa Asn Leu Arg Lys Lys Leu Ala Gly Gln	67
1 5 10	
	15

Lys .	Ala 15	Lys	Lys	Leu	Pro	Ser 20	Phe	Ser	Ser	Leu	Pro 25	Leu	Thr	Leu	Trp	
cca		act	cct	caa	ttt		gag	ctc	act	aca		gca	caa	aaa	aaa	463
Pro :																
30			110	0 1 11	35	7114	U_Lu	Deu		40	V 44 4	7.14	0111	2,5	45	
	200	taa	+	~~~		cta	aat	+ ~ ~	aat		~++	aca	200	taa		513
ttg																51.
Leu .	Arg	ПЪ	Ser	_	Ini	Leu	GIY	rrp	_	Pro	vaı	PIO	ser	_	vaı	
				50					55					60		
caa					tgaa	atgga	agg g	garaç	gttgg	gg ga	actga	aaaas	s cci	ttcaa	lara	566
Gln	Phe	Phe		Gly												
			65													
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tatg	gtca	ac c	gctt	ggaa	ia at	aktt	gaad	aca	gtac	caat	aara	tatt	tt g	gaggo	tggga	686
ktqq	tago	tc a	taco	tata	a ta	aatco	cago	act	ttat	gar	acca	aktt	ta i	agga	tcact	746
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															tgctg	180
ccct	cagg	at a	aagt	crgg	ja ec	cece	age									233
									Ala	Cys	Glu	Thr		Gly	Val	
								-30					-25			
ctt																281
Leu '	Val	Pro	Ala	His	Leu	Ser	Gly	Leu	Ile	Thr	Cys	Leu	Leu	Ala	Phe	
		-20					-15				•	-10				
tgg g	qtc	cca	acc	tcc	tat	atc	cag	aσa	tac	agt	aac	tct	cca	tta	cca	329
Trp																
	-5				0,0	1			C	5 .	O ± 3	UC1	110	LCu	10	
						_				_					10	200
ctc '	Lyac	LUCT	uc t	LCCT	.נננ	19 EC	acag	_j agaa	agg	gtac	:CC C	ccct	gtca	aaa		382
Leu			_													
															CCCC	442
															tcccc	502
agta	aact	gt a	agct	cctt	gag	ggca	agga	ttg	tgtt	gga	attt	ttgt	at t	aaca	gtgcc	562
															aaaaa	622
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<222> 673..684
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                                                                      120
ttttgttctc tgctatgctc aggacccaga tcaaaggagc tcagtaacta tttacaggcg
                                                                      180
tacatcatat gtggaggaca cttatgctgt g atg gcc cca cac aca gct tcc
                                   Met Ala Pro His Thr Ala Ser
                                       -35
ttt ggg gtc tgt ccc ctg ctc tcc gtt acc cgc gtg gta gcc act gag
                                                                      280
Phe Gly Val Cys Pro Leu Leu Ser Val Thr Arg Val Val Ala Thr Glu
                -25
                                    -20
cac tgg ctc ttc ctg gct tca ctc tct ggc atc aaa act tat cag tcc
                                                                      328
His Trp Leu Phe Leu Ala Ser Leu Ser Gly Ile Lys Thr Tyr Gln Ser
            -10
                                - 5
tac atc tca gtc ttt tgc aag gtg aca ctt atc tgattaccta attcacacra
                                                                      381
Tyr Ile Ser Val Phe Cys Lys Val Thr Leu Ile
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aggtgttaat ggtggtaatg gcataktatt tattacccca ggggacccak aacggtggta
                                                                      441
tcaaaacata tcattcccca gtggtttaaa actctggtag ctttccargg aatccaaagt
                                                                      501
ggaatccagt ctccttagct gawttcacag ggccccgtct gcacaacttg gcttctgtcg
                                                                      561
gettecetan ecetgaette ecaageetta gteateacee teteteceae ecagggetea
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aaa
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<222> 75..128

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<222> 50..244

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sed Tibloch (GAES)

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<222> 801..812

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			act Thr													154
			ttc Phe													202
			ctc Leu													250
		_	tgc Cys		_	_				_		_		-	_	298
			ggc Gly													346
gag Glu 35	agc Ser	ggc Gly	tac Tyr	aac Asn	acc Thr 40	aca Thr	gcc Ala	car Gln	acg Thr	gtc Val 45	ctg Leu	gat Asp	gac Asp	ggc	agc Ser 50	394
atc Ile	gac Asp	tay Tyr	ggc Gly	atc Ile 55	ttc Phe	caa Gln	atc Ile	aac Asn	agc Ser 60	ttc Phe	gcg Ala	tgg Trp	tgc Cys	aga Arg 65	cgc Arg	442
gga Gly	aag Lys	ctg Leu	aag Lys 70	gag Glu	aac Asn	aac Asn	cac His	tgc Cys 75	cay His	gtc Val	gcc Ala	tgc Cys	tca Ser 80	gcc Ala	ttg Leu	490
			gac Asp													538
			caa Gln													586
			gac Asp								tgt					631
taaa	ctgg	gaa c	tgga	ccca	g ga	tgct	ttgc	asc	aacc	CCC	tago	gttt	gc a	ıgtga	atgtc	691
taaactggaa ctggacccag gatgctttgc ascaacgccc taggccaaatgcctg tgtcatcttg tcccgtttcc tcccaatatt cctt																751
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ctggaaccaa cgggcacagt tggcaacacc atc atg aca tca caa cct gtt ccc 174											
Met Thr Ser Gln Pro Val Pro -65											
aat gag acc atc ata gtg ctc cca tca aat gtc atc aac ttc tcc caa 222											
Asn Glu Thr Ile Ile Val Leu Pro Ser Asn Val Ile Asn Phe Ser Gln -60 -55 -50											
gca gag aaa ccc gaa ccc acc aac cag ggg cag gat agc ctg aag aaa 270											
Ala Glu Lys Pro Glu Pro Thr Asn Gln Gly Gln Asp Ser Leu Lys Lys -45 -40 -35											
-45 -40 -35 cat cta cac qca qar rtc aaa gtt att ggg act atc cag atc ttg tgt 318											
His Leu His Ala Glu Xaa Lys Val Ile Gly Thr Ile Gln Ile Leu Cys											
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ggc atg atg gta ttg agc ttg ggg atc att ttg gca tct gct tcc ttc 366											
Gly Met Met Val Leu Ser Leu Gly Ile Ile Leu Ala Ser Ala Ser Phe											
-10 -5 1											
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5 10 15											
cca ttc ata gga ccc ttt ttt ttt atc atc tct ggc tct cta tca atc 462											
Pro Phe Ile Gly Pro Phe Phe Phe Ile Ile Ser Gly Ser Leu Ser Ile											
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55 60 65											
tct gtc aaa cag gcc acc tta aat cct gcc tca ctg cak tgt gag ttg 606											
Ser Val Lys Gln Ala Thr Leu Asn Pro Ala Ser Leu Xaa Cys Glu Leu											
70 75 80											
gmc aaa aat aat ata cca aca ara akt tat gtt yct tac ttt tat cat Yea Ive Aca											
Xaa Lys Asn Asn Ile Pro Thr Xaa Xaa Tyr Val Xaa Tyr Phe Tyr His 85 90 95											
gat toa ctt tat acc acg gac kgc tat aca gcc aaa gcc akt ctg gct 702											
Asp Ser Leu Tyr Thr Thr Asp Xaa Tyr Thr Ala Lys Ala Xaa Leu Ala											
100 105 110											
gga act etc tet etg atg etg att tge act etg etg gaa tte tge ewa 750											
Gly Thr Leu Ser Leu Met Leu Ile Cys Thr Leu Leu Glu Phe Cys Xaa											
115 120 125 130 set gtg etg etg etg etg aaa eag get tae tet gae tte 798											
sct gtg ctc act gct gtg ctg cgg tgg aaa cag gct tac tct gac ttc 798 Xaa Val Leu Thr Ala Val Leu Arg Trp Lys Gln Ala Tyr Ser Asp Phe											
135 140 145.											
cct ggg agt gta ctt ttc ctg cct cam agt tac att ggw aat tct ggm 846											
Pro Gly Ser Val Leu Phe Leu Pro Xaa Ser Tyr Ile Gly Asn Ser Gly											
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Ser											
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                         Met Gln Val Pro His Leu Arg Val Trp
                              -35
aca cag gtg awa gat acc ttc att ggt tat aga aat ttg gga ttt aca
                                                                  220
Thr Gln Val Xaa Asp Thr Phe Ile Gly Tyr Arg Asn Leu Gly Phe Thr
       -25
                          -20
                                             -15
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                                                                  268
Ser Met Cys Ile Leu Phe His Cys Leu Leu Ser Phe Gln Val Phe Lys
   -10
                      -5
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                                                                  322
Lys Lys Arg Lys Leu Xaa Leu Phe
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<213> Homo sapiens
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<222> 126..167

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<222> 726..731

<221> polyA_site <222> 743..754

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	atg gtg gcc ctg aac ctc att ctg gtt ccc tgc tgc gct gct tgg Met Val Ala Leu Asn Leu Ile Leu Val Pro Cys Cys Ala Ala Trp -10 -5 1	170
tat a	The second secon	218
	sp Pro Arg Arg Ile His Ser Gln Asp Asp Val Leu Arg Ser Ser 5 10 15	
gct g	et gat act ggg tot gcg atg cag cgg cgt gag gcc tgg gct ggt	266
Ala A	la Asp Thr Gly Ser Ala Met Gln Arg Arg Glu Ala Trp Ala Gly 20 25 30	
tgg ag	ga agg toa caa coo tto tot gtt ggt otg oot tot got gaa aga	314
Trp. A:	rg Arg Ser Gln Pro Phe Ser Val Gly Leu Pro Ser Ala Glu Arg 5 40 45	
		362
50	lu Asn Gln Pro Gly Lys Leu Ser Trp Arg Ser Leu Val Gly Glu 55 60 65	
		413
Gly H	is Arg Ile Cys Asp Leu	
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atc cca gtt cct cca agg ggc ctg ggt gct ggg gag ggg tca ggt agt

Ile Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser

Pro Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu

-35 cca gtg cgt cca cct gta tcc acc tgg ggc cct agc tgg gcc cag ctc

-50

-55

-40

60

158

206

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					Gly											302
ctc	acc	ttt	gac	ctg	ctc	cat	agg	ccc	gca	gtc	aca	ctc	tgc	cac	agc	350
					Leu											
					999											398
Ala	Asn	Phe 40	Ser	Pro	Gly	Ala	Arg 45	Val	Arg	Gly	Pro	Val 50	Lys	Val	Leu	
_	-				tac		_			_	_		_	-		446
Asp	Ser 55	Arg	Arg	Leu	Tyr	Ser 60	Cys	Lys	Trp	Val	Gln 65	Ser	Gln	Asp	Asn	
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ggcattccag gacctccgma atgatgctcc agtcccttac aagcgcttcc tggatgaggg
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tggc atg gtg ctg acc acc ctc ccc ttg ccc tct gcc aac agc cct gtg
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     Met Val Leu Thr Thr Leu Pro Leu Pro Ser Ala Asn Ser Pro Val
             -35
                                 -30
                                                                      277
aac atg ccc acc act ggc ccc aac agc ctg agt tat gct agc tct gcc
Asn Met Pro Thr Thr Gly Pro Asn Ser Leu Ser Tyr Ala Ser Ser Ala
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        -20
                            -15
ctg tcc ccc tgt ctg acc gct cca aag tcc ccc cga ctt gct atg atg
                                                                      325
Leu Ser Pro Cys Leu Thr Ala Pro Lys Ser Pro Arg Leu Ala Met Met
                        1
                                                                      374
cct gac aac taaatatcct tatccaaatc aataaarwra raatcctccc
Pro Asp Asn
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tccaraaggg tttctaaaaa caaaaaaaa a
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gaattttatc tagaaaagaa gactaagcag cttttgttct tctgtgaccc agttgctggc
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-25 -20 -15	
cet etc get tet ttg cag tgg age etg aca etg geg tgg tgt gge tec	278
Pro Leu Ala Ser Leu Gln Trp Ser Leu Thr Leu Ala Trp Cys Gly Ser	
-10 -5 1	
ggc agc cac tgg aca gag aga cca akt cag akt tca ccg tgg akt tct	326
Gly Ser His Trp Thr Glu Arg Pro Xaa Gln Xaa Ser Pro Trp Xaa Ser	
5 10 15	377
ctg tca gcg acc acc agg ggg tgatcacacg gaaggtgaac atccaggtcg	3//
Leu Ser Ala Thr Thr Arg Gly 20 25	
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Pro Ala Arg Arg His Leu Leu Val Leu Leu Leu Leu Ser Thr Leu -20 -15 -10	
gtg atc ccc tcc gct gca gct cct atc cat gat gct gac gcc caa gag	209
Val Ile Pro Ser Ala Ala Pro Ile His Asp Ala Asp Ala Gln Glu	
-5 1 5 10	
age tee ttg ggt etc aca gge etc cag age eta etc caa gge tte age	257
Ser Ser Leu Gly Leu Thr Gly Leu Gln Ser Leu Leu Gln Gly Phe Ser	
15 20 25	

20

cga ctt ttc ctg aaa ggt aac ctg ctt cgg ggc ata gac agc tta ttc

305

15

			30				35					Ser 40				
												cac His			3	53
												agc Ser			4	01
_		_	_	_	-		_					ctg Leu			4	49
												ttc Phe			4	97
		Lys										gta Val 120			5	45
												cgg Arg			5	93
												gat Asp			6	41
						_		-		_	_	cag Gln	_		6	89
cgg												daa Xaa			7	37
	_	_		tcc			_			_		amm Xaa 200			7	85
		atc Ile 205	ctc				cag		targ	gggtg	ggg 9	gacc	9999	ar	8:	35
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														aga Arg		105
		_	_	_			_		_			_		agg Arg		153
														gtg Val		201
		_	_	_	-	_			_		_			tgc Cys 5		249
														gcc Ala		297
		_		_		_		_			-	_		cag Gln		345
														tgc Cys		393
														caa Gln		441
														cca Pro 85		489
			gaa Glu 90					tgaa	aggo	ct c	9999	catgg	ga ga	acag	gctg	543
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Met Asn -60	
gca gcc atc aac acg ggc cct gcc cct gct gtc acc aag act gag act Ala Ala Ile Asn Thr Gly Pro Ala Pro Ala Val Thr Lys Thr Glu Thr -55 -50 -45	225
gag gtc cag aat cca gat gtt ctg tgg gat ttg gac atc ccc gaa gcc Glu Val Gln Asn Pro Asp Val Leu Trp Asp Leu Asp Ile Pro Glu Ala -40 -35 -30	273
agg agc cat gct gac caa gac agc aac ccc aag gcg gaa gcc ctg ctc Arg Ser His Ala Asp Gln Asp Ser Asn Pro Lys Ala Glu Ala Leu Leu -25 -20 -15	321
ccc tgc aac ctg cac tgc agc tgg ctc cac agc agc ccc agg cca gat Pro Cys Asn Leu His Cys Ser Trp Leu His Ser Ser Pro Arg Pro Asp -10 -5 1 5	369
ccc cat tcc cac ttc cca tct ktc agg agg tgc cct ttg ccc cac cct Pro His Ser His Phe Pro Ser Xaa Arg Arg Cys Pro Leu Pro His Pro	417
tgt gca acc tac ccc ccs kgc tgaaccactc tgtctcctat cctttggcca Cys Ala Thr Tyr Pro Pro Xaa	468
cctgtcctga aaggaatgtt ctcttccatt ccctcctgaa tctggcccag gaagaccata gcttcaatgy caagcctttt ccttcaaaac tgtagcctcc tctcactgaa ggtgggagct gcaggaatca ggtgcagagt aggaaatgga actaacctca ggaaggtggt attgacagag gtcaggaccc acctggatgt catgctatga aacattaaaa gaaaaaaa	528 588 648 697
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cta ctc acc tgg ctt ttc aca cta ctc ttc ttg atc atg ttg gtg ttg Leu Leu Thr Trp Leu Phe Thr Leu Leu Phe Leu Ile Met Leu Val Leu -15 -10 -5	222
aaa ctg gat gag aaa gca cct tgg aac tgg ttc ctc ata ttc att cca Lys Leu Asp Glu Lys Ala Pro Trp Asn Trp Phe Leu Ile Phe Ile Pro	270
gtc tgg ata ttt gat act atc ctt ctt gtc ctg ctg att gtg aaa atg Val Trp Ile Phe Asp Thr Ile Leu Leu Val Leu Leu Ile Val Lys Met	318

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Ala Gly Arg Cys Lys Ser Gly Phe Asp Leu Asp Met Asp His Thr Ile
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gggccttgct ggctggggct ttaacagaac tcggatataa tgtctttttt gtgaaagact
                                                                      546
                                                                      606
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                                                                      666
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ccaaagcagc actcgttgcc aattagggaa tggaccgttt gggttccttt agca atg
                                                                      177
                                                                      225
atc cct ctg ata age cac ctt gcc gag gct gct cct cct acc tca tgg
Ile Pro Leu Ile Ser His Leu Ala Glu Ala Ala Pro Pro Thr Ser Trp
            -30
                                -25
age ett ata tea agt gtg etg aat gtg gge eac ete ett tet tee tet
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Ser Leu Ile Ser Ser Val Leu Asn Val Gly His Leu Leu Phe Ser Ser
                            -10
                                                -5
gct tgc agt gtt tca ctc gag gct ttg agt aca aga aac atc aaa gcg
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Ala Cys Ser Val Ser Leu Glu Ala Leu Ser Thr Arg Asn Ile Lys Ala
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ate ata ett atg aaa taatggette agatttteet gteettgate eeagetggae
Ile Ile Leu Met Lys
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ggatgtagcc aatcaaatgt gcaccaarac caaggaggag tgtgagaagc actatatgaa
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gcatttcatc aataacccyc tgtttgcatc trscctgctg aacctgaaac aascagrgga
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                                           -30
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                                                                      277
Ser Val Ala Cys Ser Phe Ala Val Gly Ala Gly Phe Leu Ala Phe Leu
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                                        -15
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                                                                      325
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                - 5
                                    1
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Gly Thr Arg Phe Lys Thr Ala Phe Gln Leu Leu Asp Phe Ile Leu Ala
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                            15
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Val Leu Trp Ala Val Val Trp Phe Met Gly Phe Cys Phe Leu Ala Asn
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caa tgg cag cat tcg ccg ccc aaa gar kkc ctc ctg ggg agc agc agt
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Gln Trp Gln His Ser Pro Pro Lys Glu Xaa Leu Leu Gly Ser Ser Ser
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                    45
gcc cag gca gcc atc ggc stt cac ctt ctt ctc cat cct tgt ctg gat
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Ala Gln Ala Ala Ile Gly Xaa His Leu Leu His Pro Cys Leu Asp
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Ile Pro Xaa Leu Pro Gly Xaa Pro Gly Pro Pro Lys
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etgecetgte eccetgtetg accgetemaa agtececeg gettgetatg atgeetgaca
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1112

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Gln Thr Ser Pro Val Leu Leu Ala Ser Leu Gly Val Gly Leu Val Thr
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                                -15
                                                     -10
ctg ctc ggc ctg gct gtg ggc tcc tac ttg gtt cgg agg tcc cgc cgg
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Leu Leu Gly Leu Ala Val Gly Ser Tyr Leu Val Arg Arg Ser Arg Arg
cct cag gtc act ctc ctg gac ccc aat gaa aag tac ctg cta cga ctg
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Pro Gln Val Thr Leu Leu Asp Pro Asn Glu Lys Tyr Leu Leu Arg Leu
                   15
                                        20
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Leu Asp Lys Thr Thr Val Ser His Asn Thr Lys Arg Phe Arg Phe Ala
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ctg ccc acc gcc cac cac act ctg ggg ctg cct gtg ggc aaa cat atc
Leu Pro Thr Ala His His Thr Leu Gly Leu Pro Val Gly Lys His Ile
                                50
                                                     55
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Tyr Leu Ser Thr Arg Ile Asp Gly Ser Leu Val Ile Arg Pro Tyr Thr
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cct gtc acc agt gat gag gat caa ggc tat gtg gat ctt gtc mtc aag
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Pro Val Thr Ser Asp Glu Asp Gln Gly Tyr Val Asp Leu Val Xaa Lys
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gtc tac ctg aag ggt gtg cac ccc aaa ttt cct gag gga ggg aar atg
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Val Tyr Leu Lys Gly Val His Pro Lys Phe Pro Glu Gly Gly Lys Met
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tct cak tac ctg gat asc ctg aaa gtt ggg gat btg gtg gaa ttt csg
Ser Xaa Tyr Leu Asp Xaa Leu Lys Val Gly Asp Xaa Val Glu Phe Xaa
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                                     115
ggg cca agc ggg ttg ctc act tac act gga aaa ggg cat ttt aac att
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Gly Pro Ser Gly Leu Leu Thr Tyr Thr Gly Lys Gly His Phe Asn Ile
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Gln Pro Asn Lys Asn Leu His Gln Asn Pro Glu Trp Arg Arg Asn Trp
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aagetetggt teactetgga teateceeca aaagrttggg cetacageaa gggetttgtg
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876

936

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tcc att tct gag ctc tgc aag gga caa gaa cta gag cca tca ggg gct 296

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acc Thr 40	ctg	cct Pro	tgg Trp	ctg Leu	cta Leu 45	cag	ctt Leu	ttt Phe	cac His	tcc Ser 50	act	gcc Ala	cta Leu	rgg Xaa	gna Xaa 55	392
dtt					gga									tcc Ser 70		440
gct Ala	ccr Pro	rgt Xaa	cca Pro 75	rca Xaa	acc Thr	tgc Cys	acc Thr	ctg Leu 80	gaa Glu	cca Pro	gga Gly	gtg Val	gac Asp 85	cct Pro	acc Thr	488
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atco	cago	cac t	ttgg	ggagg gtgaa	gc ca	aggi	tggg(aga aca	atcgo aaaa	cctg atar	aggt gaaa	tctg aatt:	gag 1	ttca: caggi	cctgta agacca tgtggt	700 760 820
ggat	gcgg	gag g	gtitgo	cagt	ca go ga go aa aa	ccga	gatt	g aga g tgo	actga	aggc	ctc	agaat	ttc (ggcga	accca	880 940 968
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tac	tgat	cta	tnna	tggc	ag a	gaaa	aaaa	a at	tgtg	acca	gag	acgt	gta	gcaa	tgaaca	120
agg	aacr	cca '	ca a M	et X	wn n aa X 70	aa P	he T	ca g hr A	sp P	cc t ro S 65	er S	er V	al A	sn G	aa aag lu Lys 60	171
aag Lys	agg Arg	agg Arg	gag Glu -55	Arg	gaa Glu	gaa Glu	agg Arg	cag Gln -50	Asn	att Ile	gtc Val	ctg Leu	tgg Trp -45	aga Arg	cag Gln	219

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Lys Glu Trp Thr Ser Lys Leu Trp His Arg Gln Ser Ile Val Val Ser
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Phe Leu Leu Leu Ala Gly Leu Ile Ala Thr Tyr Tyr Val Glu Gly
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                                                                     411
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Val His Gln Gln Tyr Val Gln Arg Ile Glu Lys Gln Phe Leu Leu Tyr
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Ala Tyr Trp Ile Gly Leu Gly Ile Leu Ser Ser Val Gly Leu Gly Thr
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Gly Leu His Thr Phe Leu Leu Tyr Leu Gly Pro His Ile Ala Ser Val
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                                                                     555
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Thr Leu Ala Ala Tyr Glu Cys Asn Ser Val Asn Phe Pro Glu Pro Pro
                    60
                                        65
                                                                      603
tat cct gat cag att att tgt cca gat gaa gag ggc act gaa gga acc
Tyr Pro Asp Gln Ile Ile Cys Pro Asp Glu Glu Gly Thr Glu Gly Thr
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                75
att tot ttg tgg agt atc atc tca aaa gtt agg att gaa gcc tgc atg
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Ile Ser Leu Trp Ser Ile Ile Ser Lys Val Arg Ile Glu Ala Cys Met
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Trp Gly Ile Gly Thr Ala Ile Gly Glu Leu Pro Pro Tyr Phe Met Ala
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Arg Ala Ala Arg Leu Ser Gly Ala Glu Pro Asp Asp Glu Glu Tyr Gln
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Glu Phe Glu Glu Met Leu Glu His Ala Glu Ser Ala Gln Val Arg Thr
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Val Gly Ile Glu Asn Arg Thr Leu Tyr Phe Phe Leu Lys Arg Leu Leu
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ccca	agaa	iga (ctggg	gga a	atg g	gag a	aga d	cag t	ca a	199	JCC e	acg (ca y	gaa a	aay	170
				ı	iet (_	in s	ser A	arg v			ser (Glu I	n y S	
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	Phe	Leu	Leu	Ile		Thr	Ile	Leu	Thr		Trp	Leu	Pne	Lys	Asn	
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His	Arg	Phe	-	Phe	Leu	His	Glu		GIÀ	GIA	Ala	Met		Tyr	GIY	
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ctt	aya	atg	gga	cta	att	tta	csa	tat	gct	aca	gca	cca -	act	gat	att	362
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gaa	agt	ggr	rct	gtc	tat	gac	tgt	gta	aaa	cta	act	ttc	agt	cca	tca	410
Glu		Gly	Xaa	Val	Tyr		Cys	Val	Lys	Leu		Phe	ser	Pro	Ser	
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	Leu	Leu	Val	Asn		Thr	Asp	Gln	Val		Glu	Tyr	гàг	Tyr		
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Arg	Glu	Ile	Ser		His	Xaa	He	Asn		His	Xaa	GIY	Asn	Ala	TTE	
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Leu	GIU	Lys		Thr	Pne	Asp	Pro		11e	Pne	Pne	Asn		Leu	Leu	
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cca	cca	att	ata	בבב	cat	gca	gga	cat	agt	cta	aag	aag	aga	cac	Dho	602
Pro	Pro		тте	Pne	HIS	Ala		Tyr	ser	Leu	гÀг		Arg	His	Phe	
		105				- 4- 4-	110					115		- at	~~~	650
														act		650
Pne		ASI	Leu	GIA	Ser		ьеи	IIII	TYL	AId		neu	GIY	Thr	MIG	
	120		-4			125			~~+		130		-++a	a a a a t	-	701
_						_	Laag	Juga	Jac	ccgg	gett	a a	acca.	caggt	-	,01
135	ser	Cys	Ile	vai	140	GIY										
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gget	-9-5	399	ttyg:	-yac	3L 91	-9 - 9 ·	2999	a CC		2000	+++	Syac	727	ttaat	tccac	821
gaad		300			ar c	-+	nata:		~~>>	acyc	W200		sac	acact	ttctc	881
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																1001
															cttgtc	1061
															caagag	1121
															atatca	1181
															actctt	1241
															actetg cetetg	1301
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caa atg agc atg caa ttc ttg ttt aag atg gtg gcc tta tgc tgt tgt
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Leu Trp Lys Ile Ser Gly Cys Glu Glu Val Pro Leu Thr Tyr Asn Leu
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ctc aag tgc ctc cta gat aaa gcg cac tgt gta ctc ctg aca cct tgt
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Leu Lys Cys Leu Leu Asp Lys Ala His Cys Val Leu Leu Thr Pro Cys
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Gly Tyr Ile Phe Ser Leu Ile Ser Pro Glu Ile Leu Lys Leu Thr Leu
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Leu Thr Val Ser Ser Xaa Cys Val His Arg Ser Ser Ala Arg Lys Glu
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Lys
75
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Met Arg
raa aag tgg aaa atg gga gge atg aaa tac atc ttt teg ttg tte 165
Xaa Lys Trp Lys Met Gly Gly Met Lys Tyr Ile Phe Ser Leu Leu Phe
-25 -20 -15 -10
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Phe Leu Leu Glu Gly Gly Xaa Thr Glu Gln Val Xaa His	Ser Glu
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Thr Tyr Cys Met Phe Gln Asp Lys Lys Tyr Arg Val Gly Glu	
10 15 20	
cat cct tac ctg gaa cct tat ggg ttg gtt tac tgc gtg aac	tgc atc 309
His Pro Tyr Leu Glu Pro Tyr Gly Leu Val Tyr Cys Val Asn 25 30 35	Cys Ile
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Cys Ser Glu Asn Gly Asn Val Leu Cys Ser Arg Val Arg Cys	
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Val His Cys Leu Ser Pro Val His Ile Pro His Leu Cys Cys	Pro Arg
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Cys Pro Glu Asp Ser Leu Pro Pro Val Asn Asn Xaa Val Thr	Ser
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115

435

485

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296

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Met Gly Trp Gln Arg	
tgg tgg tgc ttt cat ctt cag gca gaa gcc tct gcc cat ccc cct caa Trp Trp Cys Phe His Leu Gln Ala Glu Ala Ser Ala His Pro Pro Gln -10 -5 1	344
ggg ctg cag gcc caa ttc tca tgc tgc cct tgg gtg ggc atc tgt Gly Leu Gln Ala Gln Phe Ser Cys Cys Pro Trp Val Gly Ile Cys 5 10 15	389
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cagattitigg ggaggcotta gtacggo atg atg agt tot gag ota ogg agg aac	234
Met Met Ser Ser Glu Leu Arg Arg Asn -25	
cct cat ttc ctc aaa agt aat tta ttt tta cag ctt ctg gtt tca cat	282
Pro His Phe Leu Lys Ser Asn Leu Phe Leu Gln Leu Leu Val Ser His	
-20 -15 -10 -5	
gaa att gtt tgc gct act gag act gtt act aca aac ttt tta aga cat	330
Glu Ile Val Cys Ala Thr Glu Thr Val Thr Thr Asn Phe Leu Arg His	

gaa aag gcg taatgaaaac catcccgtcc ccattcctcc tcctctctga 379 Glu Lys Ala 15 gggactggag ggaagccgtg cttctgagga acaactctaa ttagtacact tgtgtttgta ratttacacw wtgtattatg tattaacatg gcgtgtttat ttttgtattt ttctctggtt gggagtatka tatgaaggat caarateete aacteacaca tgtaracaaa cattasetet ttactctttc tcaacccctt wtatgatttt aataattctc acttaactaa ttttgtaagc 619 ctgagatcaa taagaaatgt tcaggagaga ggaaagaaaa aaaatatatg ctccacaatt 679 tatatttaga gagagaacac ttagtcttgc ctgtcaaaaa gtccaacatt tcataggtag 739 taggggccac atattacatt cagttgctat aggtccagca actgaacctg ccattacctg 799 ggcaaggaaa gatccctttg ctctaggaaa gcttggccca aattgatttt cttcttttc 859 cccctgtagg actgactgtt ggctaatttt gtcaagcaca gctgtggtgg gaagagttag 919 ggccagtgtc ttgaaaatca atcaagtagt gaatgtgatc tctttgcara gctatagata 979 1039 gggtgtgcat ctgttgaaat gctcaagact taattatttg ccttttgaaa tcactgtaaa 1099 tgcccccatc cggttcctct tcttcccarg tgtgccaagg aattaatctt ggtttcacta 1159 caattaaaat tcactccttt ccaatcatgt cattgaaagt gcctttaacg aaagaaatgg 1219 tcactgaatg ggaattetet taagaaacce tgagattaaa aaaagactat ttggataact tataggaaag cctagaacct cccagtagag tggggatttt tttcttcttc cctttctctt 1339 ttggacaata gttaaattag cagtattagt tatgagtttg gttgcagtgt tcttatcttg 1399 tgggctgatt tccaaaaacc acatgctgct gaatttacca gggatcctca tacctcacaa 1459 tgcaaaccac ttactaccag gcctttttct gtgtccactg gagagettga gctcacactc 1519 aaagatcaga ggacctacag agagggctct ttggtttgag gaccatggct tacctttcct 1579 gcctttgacc catcacaccc catttcctcc tctttccctc tccccgctgc caaaaaaaaa 1639 1641 <210> 353 <211> 884 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 69..557 <221> sig_peptide <222> 69..224 <223> Von Heijne matrix score 4.69999980926514 seg LGLALGRLEGGSA/RH <221> polyA signal <222> 849..854 <221> polyA_site <222> 870..883 <400> 353 attggctccg gatcgtgcgt gaggcggctt cgtgggcagc gagagtcaca gacaagacag 60 caagcagg atg gag cac tac cgg aaa gct ggc tct gta gag ctc cca gcg 110 Met Glu His Tyr Arg Lys Ala Gly Ser Val Glu Leu Pro Ala -50 -45 cet tee cea atg eee cag eta eet eet gat ace ett gag atg egg gte 158 Pro Ser Pro Met Pro Gln Leu Pro Pro Asp Thr Leu Glu Met Arg Val -35 -30 cga gat ggc agc aaa att cgc aac ctg ctg ggg ttg gct ctg ggt cgg 206 Arg Asp Gly Ser Lys Ile Arg Asn Leu Leu Gly Leu Ala Leu Gly Arg -20 -15 -10 ttg gag ggc ggc agt gct cgg cat gta gtg ttc tca ggt tct ggc agg 254

Leu Glu Gly Gly Ser Ala Arg His Val Val Phe Ser Gly Ser Gly Arg

	-5					1				5					10 .	
														cgg Arg 25		302
			His	cag				Leu	ckt				Thr	gag Glu		350
		Val					Asp					Pro		aca Thr		398
	Arg					Xaa					Xaa			ccc Pro		446
Asp					Gly					Gly				ggc Gly	Leu	494
				Ser					Pro					agg Arg		542
			Arg	_	tgaa	aaaco	etg o	ctgas	100 sccas	gc ct	gtto	etccs	999	105 cctra	aatg	597
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	.> pc		site 29	:												
atca tgta	atgo	ct t	tccc ct a	ctaa itg d	ac to cat <u>c</u> lis C	eccto ggt t	gtts tt s	g cta gaa a	acat ta a	taa ta t le S	cttc cc t Ser I	ctta tg a	ag t			60 120 169
					gtg					ttg				act Thr		217
~~~					-50					~ 2 3					20	265

ggc tca tca tca cca gtg acc tgg ttg ggc cta ctc tcc ttc cag aac Gly Ser Ser Pro Val Thr Trp Leu Gly Leu Leu Ser Phe Gln Asn

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-10

-15

265

Leu His Cys Phe Pro Asp Leu Pro Thr Glu Met Pro Leu Xaa Ala Lys 1 5 10	
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ttgcttcatc taggtccagg ccccaaktag cttgctgaag gaacttaaaa agtagctgtt attattgta ttgtataasc taaaacatt tatttttgtt gaatcraaac aattccatgt ascaatcttt tttctgttca cggtgtttgt gataaaacct taaattccgc aagcatcagt tttttgaaaa aatgggaatt gaccggatag wwacaggcaa agwtataaat agctacaaca tcatttaact tttataaaca tgccttctct ctattgaara catctgatat ttttgctgga aagttggatc tatcctcagt aactctgcca tgaattcctg tttcckggtt ccaaaaaaaa aaaa	425 485 545 605 665 725 729
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agtttccaag ggaaggagca gcgtgtggga aagcacagaa gagtgagaag gaagcgacta aattttattt actttct atg cat cat ggc ctc aca cca ctg tta ctt ggt  Met His His Gly Leu Thr Pro Leu Leu Leu Gly  -50  -45  -40  gta cat gag caa aaa cag caa gtg gtg aaa ttt tta atc aag aaa aaa Val His Glu Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys Lys	110
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501	21.44			110					115			1		120		
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_			_	_										Thr		
ASP	ASII	GIY	_	Asp	GIY	Deu	116	130	PIO	naa	цуѕ	Add	135	1111	110	
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		_														971
	_	•	_				_		_		_	Jayco	ag	ccaai	raraaa	1013
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Call Leu Xaa Arg Xaa Asp Arg Xaa Pro Ser Asn Met Xaa Thr Lys Tyr 75 80 85 85 85 85 85 85 85 85 85 85 85 85 85		55					60					65					
Call Leu Xaa Arg Xaa Asp Arg Xaa Pro Ser Asn Met Xaa Thr Lys Tyr 70	gaa	cta	rat	cga	gsk	gat	aga	rac	cct	agt	aac	atg	twt	acc	aaa	tac .	345
tac att cac cga att cca ara agc cgg gag gtt cag cag tcc tgg ccc Tyr Ile His Arg Ile Pro Xaa Ser Arg Glu Val Gln Gln Ser Trp Pro 90 100 tcc acc gtt tyc acc acc ttg cac tcc atg tgg ctc tcc ttk ccc cta 105 110 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 115 110 110																	
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90 95 100  tcc acc gtt tyc acc acc ttg cac tcc atg tgg ctc tcc ttk ccc cta 441  Ser Thr Val Xaa Thr Thr Leu His Ser Met Trp Leu Ser Xaa Pro Leu 105  att cac agg gtg aag cca rat ttg gtg ttg tgt aac gga cca gga aca 489  Ile His Arg Val Lys Pro Xaa Leu Val Leu Cys Asn Gly Pro Gly Thr 120  tgt gty cct atc tgt gta tct gcc ctt ctc ctt ggg ata cta gga ata 537  Cys Val Pro Ile Cys Val Ser Ala Leu Leu Leu Gly Ile Leu Gly Ile 115  aag aaa gtg atc att gtc tac gtt gaa ag cat tgc cgt gta aaa acs 585  Lys Lys Val Ile Ile Val Tyr Val Glu Ser Ile Cys Arg Val Lys Thr 150  tta tcc atg tcc gga aag att ctg ttt cat ctc tca att ctc att 633  Leu Ser Met Ser Gly Lys Ile Leu Phis Leu Ser Ann Tyr Phe Ile 170  gtt cag tgg ccg gct ctg aaa gaa att cca aaa tcg gg tac ctt Val Glu Trp Pro Ala Leu Lys Glu Lys Tyr Pro Lys Ser Val Tyr Leu 185  ggg cga att gtt tgacaaatgg caactgactt ctttagaatt ttgcasttaa 681  Arg Ile Val 200  cagtartatg tactcaaatt ggggggaaaa aaaccctaca tgtttcttg aaagggctct gacaactgactct garaattattg atggtaagga ataaaacatg twcagatrac tcagtgaara ascactgaagtct tctttatga aacaacatt gataaacata actacyaat gtttatgcct garaactaaggct ttctttatga aacaacatt gataaacgta actacyaaat gtttatgcct 973  gacagtcctg araattattg atggtaagga ataaaacatg twcagatrac tcagtgaara 853  c210> 357  c211> 868  c222> 126527  c221> sig_peptide  c222> 126527  c221> polyA_signal	tac	att	cac	cga	att	cca	ara	agc	cgg	gag	gtt	cag	cag	tcc	tgg	ccc	393
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Ser Thr Val Xaa Thr Thr Leu His Ser Met Trp Leu Ser Xaa Pro Leu 105																	
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### Arg Val Lys Pro Xaa Leu Val Leu Cys Asn Gly Pro Gly Thr 120 125 130  ### Tay Val Lys Pro Xaa Leu Val Leu Cys Asn Gly Pro Gly Thr 120 125 130  ### Tay Val Lys Pro Xaa Leu Val Leu Cys Asn Gly Pro Gly Thr 120 125 130  ### Tay Val Lys Gly Ere Ctt ctc ctt ggg ata cta gga ata Cys Val Pro Ile Cys Val Ser Ala Leu Leu Leu Gly Ile Leu Gly Ile Leu Gly Ile 135 140 145 145  ### Tay Val I Ile Cys Val Ser Ala Leu Leu Leu Leu Gly Ile Leu Gly Ile 135 140 145  ### Tay Val Ile Ile Val Tyr Val Glu Ser Ile Cys Arg Val Lys Thr 150 160 165  ### Tay Val Ile Ile Val Tyr Val Glu Ser Ile Cys Arg Val Lys Thr 150 160 165  ### Tay Val Cys Ile Leu Phe His Leu Ser Asn Tyr Phe Ile 170 175 180  ### Tay Val Glu Lys Tyr Pro Lys Ser Val Tyr Leu 185 190 195  ### Tay Val Glu Lys Tyr Pro Lys Ser Val Tyr Leu 185  ### Tay Ile Val 200  ### Cag try Cys Arg Val Lys Tyr Pro Lys Ser Val Tyr Leu 185  ### Tay Ile Val 200  ### Tay Ile Val 200  ### Cag try Cys Arg Val Lys Tyr Pro Lys Ser Val Tyr Leu 200  ### Tay Ile Val 200  ##	Ser	Thr	Val		Thr	Thr	Leu	His	Ser	Met	Trp	Leu	Ser	Xaa	Pro	Leu	
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-10

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_	_	_	gct Ala	_										_		314
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ara	arat	gtt	catc	ggaa	ct a	araa	tgak	t tt	aaca	ggtc	agt	tttt	tga	gtga	atgto	19	540
gaa	araa	cac	agca	taca	ga a	tggc	taac	c at	gaaa	gttc	atg	aaag	cgt	кgaa	aaaat	.C	600 654
aaa	ccaa	atc	ataa	ttag	at a	cgaa	gca M	et L	eu X	aa L	eu S	ca a er A	rg A	la T	ca aa hr Ly -2	/S	4
~ ^ ~	~~-						 -		~+~		25	~~~	++			. 0	702
rac	ggc	cgg	gcg	ogg	1 499 1 Tre	Len	Met	Pro	yca Val	alC alT	Pro	Ala	Len	. Cay ı Gln	gag Glu		, 02
-144	. Cly	-11 G	,a	-15					-10					~5			
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Trp Arg Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn 35 40 45	202
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Leu Thr Ser Ser Ser Ser Val Arg Val Glu Trp Ile Ala Ala Val Thr
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                                  -15
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Gln Thr Gly His Met Arg Met Ala Ala Leu Leu Pro Gln 45	
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ctttaagaca aaacatgact gaaaagagca cctgtacttt tcaagccact ggagggagaa	1095
atggaaaaca tgaaaacagc aatcttctta tgcttctgaa taatcaaaga ctaatttgtg	1155
attttacttt ttaatagata tgactttgct tccaacatgg aatgaaataa aaaataaata	1215
ataaaagatt gccatgaatc ttgcaaaaaa aaaaa	1250

<210> 376

<211> 947

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<221> polyA_site <222> 937..947

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ccttgacctg accgacactg gttcccatga agcggctac	c aaagctgttc tccaggagtt 120
tggtagaatc gacattctgg tcaacaatgg tgga atg	tcc cag cgt tct ctg tgc 175
Met	Ser Gln Arg Ser Leu Cys
	-60
atg gat acc agc ttg gat gtc tac aga rag ct	
Met Asp Thr Ser Leu Asp Val Tyr Arg Xaa Le	
-55 -50 -4	3
tta ggg acg gtg tcc ttg aca aaa tgt gtt ct Leu Gly Thr Val Ser Leu Thr Lys Cys Val Le	y Dro His Met The Glu
-35 -30	-25
agg aag caa gga aag att gtt act gtg aat ag	
Arg Lys Gln Gly Lys Ile Val Thr Val Asn Se	r The Leu Gly The The
-20 -15	-10
tot gta cot ott too att gga tac tgt got ag	c aag cat gct ctc cgg 367
Ser Val Pro Leu Ser Ile Gly Tyr Cys Ala Se	
-5 1	5
ggt ttt ttt aat ggc ctt cga aca gaa ctt gc	c aca tac cca qqt ata 415
Gly Phe Phe Asn Gly Leu Arg Thr Glu Leu Al	
10 15 20	
ata gtt tct aac att tgc cca gga cct gtg ca	a tca aat att gtg gaa 463
Ile Val Ser Asn Ile Cys Pro Gly Pro Val Gl	
30 35	40
aat tcc cta gct gga gaa gtc aca aaa act at	a ggc aat aat gga aac 511
Asn Ser Leu Ala Gly Glu Val Thr Lys Thr Il	e Gly Asn Asn Gly Asn
45 50	55
cag tcc cac aag atg aca acc agt cgt tgt gt	g cgg ctg atg tta atc 559
Gln Ser His Lys Met Thr Thr Ser Arg Cys Va	l Arg Leu Met Leu Ile
60 65	70
agc atg gcc aat gat ttg aaa gaa gtt tgg at	c tca gaa caa cct ttc 607
Ser Met Ala Asn Asp Leu Lys Glu Val Trp Il	
75 80	85
ttg tta gta aca tat ttg tgg caa tac atg cc	
Leu Leu Val Thr Tyr Leu Trp Gln Tyr Met Pr	
90 95 10	- T
ata acc aac aag atg ggg aag aaa agg att ga	.5 446 666 445 456
Ile Thr Asn Lys Met Gly Lys Lys Arg Ile Gl	u Ash Phe Lys Ser Gly 120
110 115	
gtg gat gcm rac tct tct tat ttt aaa atc tt	
Val Asp Ala Xaa Ser Ser Tyr Phe Lys Ile Ph	135
125 130	
tgaaaaganc acctgtactt ttcaagccac tggagggag	,
caatcttctt atgcttctga ataatcaaag actaatttg	,
atgactttgc ttccaacatg grrtgaaata aaaaataaa	947
cttgcaaaaa aaaaaa	747

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<211> 621 <212> DNA

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<222> 46..585

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<210> 378

<222> 46..120

<211> 52

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<222> -20..-1

<400> 378

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                              -15
Arg Ala Phe Ala Cys Arg Gly Cys Gln Leu Ala Pro Glu Arg Gly Ala
    -5
Glu Arg Arg Asp Thr Ala Pro Ser Gly Val Ser Arg Phe Cys Pro Pro
                                     20
                  15
Arg Lys Ser Cys His Asp Trp Ile Gly Pro Pro Asp Lys Tyr Ser Asn
              30
                                35
Leu Arg Pro Val His Phe Tyr Ile Pro Glu Asn Glu Ser Pro Leu Glu
                             50
Gln Lys Leu Arg Lys Leu Arg Gln Glu Thr Gln Glu Trp Asn Gln Gln
                         65
Phe Trp Ala Asn Gln Asn Leu Thr Phe Ser Lys Glu Lys Glu Glu Phe
            80
Ile His Ser Arg Leu Lys Thr Lys Gly Leu Gly Leu Arg Thr Glu Ser
                                     100
                 95
Gly Gln Lys Ala Thr Leu Asn Ala Glu Glu Met Ala Asp Phe Tyr Lys
                                  115
                                                    120
               110
Glu Phe Leu Ser Lys Asn Phe Gln Lys His Met Tyr Tyr Asn Arg Asp
           125
                              130
Trp Tyr Lys Arg Asn Phe Ala Ile Thr Phe Phe Met Gly Lys Val Ala
                                             150
                         145
Leu Glu Arg Ile Trp Asn Lys Leu Lys Gln Lys Gln Lys Lys Arg Ser
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Asn
170
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<210> 380
<211> 82
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -14..-1
<400> 380
Met Ala Phe Thr Leu Xaa Ser Leu Leu Gln Ala Ala Leu Leu Cys Val
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-10

<210> 381 <211> 198 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 <400> 381 Met Pro Val Pro Ala Leu Cys Leu Leu Trp Ala Leu Ala Met Val Thr -10 -15 Arg Pro Ala Ser Ala Ala Pro Met Gly Gly Pro Glu Leu Ala Gln His 1 Glu Glu Leu Thr Leu Leu Phe His Gly Thr Leu Gln Leu Gly Gln Ala 20 15 Leu Asn Gly Val Tyr Arg Thr Thr Glu Gly Arg Leu Thr Lys Ala Arg 35 Asn Ser Leu Gly Leu Tyr Gly Arg Thr Ile Glu Leu Leu Gly Gln Glu 50 Val Ser Arg Gly Arg Asp Ala Ala Gln Glu Leu Arg Ala Ser Leu Leu 70 65 Glu Thr Gln Met Glu Glu Asp Ile Leu Xaa Leu Gln Ala Xaa Ala Thr Ala Glu Val Leu Gly Glu Val Ala Gln Ala Gln Lys Val Leu Arg Asp 100 Ser Val Gln Arg Leu Xaa Xaa Gln Leu Xaa Xaa Ala Trp Leu Gly Pro 120 115 Ala Tyr Arg Lys Phe Glu Val Leu Lys Ala Pro Pro Xaa Lys Gln Asn 135 130 His Ile Leu Trp Ala Leu Thr Gly His Val Xaa Arg Gln Xaa Arg Glu 145 150 Met Val Ala Gln Gln Xaa Xaa Leu Xaa Gln Ile Gln Glu Lys Leu His Thr Ala Ala Leu Pro Ala 175

<210> 382 <211> 160 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -55..-1

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-50 -45 Ser Gly Leu Ser Glu Val Val Glu Ala Ser Ser Leu Ser Trp Ser Thr -30 -25 · -35 Arg Ile Lys Gly Phe Ile Ala Cys Phe Ala Ile Gly Ile Leu Cys Ser -20 -15 Leu Leu Gly Thr Val Leu Leu Trp Val Pro Arg Lys Gly Leu His Leu Phe Ala Val Phe Tyr Thr Phe Gly Asn Ile Ala Ser Ile Gly Ser Thr 20 Ile Phe Leu Met Gly Pro Val Lys Gln Leu Lys Arg Met Phe Glu Pro 30 35 Thr Arg Leu Ile Ala Thr Ile Met Val Leu Leu Cys Phe Ala Leu Thr 50 Leu Cys Ser Ala Phe Trp Trp His Asn Lys Gly Leu Ala Leu Ile Phe 65 Cys Ile Leu Gln Ser Leu Ala Leu Thr Trp Tyr Ser Leu Ser Phe Ile 85 80 Pro Phe Ala Arg Asp Ala Val Lys Xaa Cys Phe Ala Val Cys Leu Ala 95 100

<210> 383 <211> 108 <212> PRT <213> Homo sapiens <220>

<221> SIGNAL <222> -18..-1

<400> 383

 Met
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 Leu
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 Gly
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 Val

 Ser
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 Thr
 Leu
 Cys
 Ser
 Met
 Glu
 Glu
 Ala
 Ile
 Arg
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 Ile
 Ala
 Ile
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Met Ile Ser Arg Gln Leu Arg Ser Leu Ser Cys Leu Cys Pro Ala Leu
-20 -15 -10
Phe Pro GIy Thr Ser Ser Phe Ile Val Ala Leu Ser Ser Pro Ala Asp

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1
   - 5
Leu Tyr Ile Pro Xaa Arg Xaa Arg Ser Asp Glu Leu Val Phe Glu Ser
                     20 25 ·
          15
Gln Lys Gly Ser Ala Met Glu Leu Ala Val Ile Thr Val Xaa Gly Val
                  35
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<210> 385
<211> 27
<212> PRT
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<222> -15..-1
<400> 385
Met Gly Phe Leu Xaa Leu Met Thr Leu Thr Thr His Val His Ser Ser
                         -5
-15 -10
Ala Lys Pro Asn Glu Gln Pro Trp Leu Leu Asn
       5
                           10
<210> 386
<211> 186
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -21..-1
<400> 386
Met Ser Pro Ser Gly Arg Leu Cys Leu Leu Thr Ile Val Gly Leu Ile
                                      -10
                     -15
Leu Pro Thr Arg Gly Gln Thr Leu Lys Asp Thr Thr Ser Ser Ser
                 1
Ala Asp Ser Thr Ile Met Asp Ile Gln Val Pro Thr Arg Ala Pro Asp
                           20
Ala Val Tyr Thr Glu Leu Gln Pro Thr Ser Pro Thr Pro Thr Trp Pro
                      35
    30
Ala Asp Glu Thr Pro Gln Pro Gln Thr Gln Thr Gln Gln Leu Glu Gly
 45
                  50
Thr Asp Gly Pro Leu Val Thr Asp Pro Glu Thr His Xaa Ser Xaa Lys
                                   70
                 65
Ala Ala His Pro Thr Asp Asp Thr Thr Thr Leu Ser Glu Arg Pro Ser
                               85
Pro Ser Thr Xaa Val His Xaa Arg Pro Xaa Xaa Pro Ser Xaa His Leu
                           100
                                             105
          95
Val Phe Met Arg Met Thr Pro Ser Ser Met Met Asn Thr Pro Ser Gly
                        115
                                          120
Asn Xaa Gly Cys Trp Ser Gln Leu Cys Cys Ser Ser Gln Ala Ser Ser
                     130
                                       135
 Ser Ser Pro Val Ala Ser Ala Gly Ser Cys Pro Gly Tyr Ala Gly Ile
                                   150
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165

Ile Ala Gly Glu Ser Ile Arg Asn Arg Ser 160

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<211> 179
<212> PRT
<213> Homo sapiens
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<400> 387
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                                          -15
Leu Leu Cys Gly Pro Ser Gln Asp Gln Cys Arg Pro Val Leu Gln Asn
                   - 5
Leu Leu Gln Ser Pro Gly Leu Thr Trp Ser Leu Glu Val Pro Thr Gly
          10
Arg Glu Gly Lys Glu Gly Gly Asp Arg Gly Pro Gly Leu Xaa Gly Ala
Thr Pro Ala Arg Ser Pro Gln Gly Lys Glu Met Gly Arg Gln Arg Thr
                        45
Arg Lys Val Lys Gly Pro Ala Trp Xaa His Thr Ala Asn Gln Glu Leu
                                       65
                    60
Asn Arg Met Arg Ser Leu Ser Ser Gly Ser Val Pro Val Gly His Leu
                                   80
Glu Gly Gly Thr Val Lys Leu Gln Lys Asp Thr Gly Leu His Ser Cys
                               95
Xaa Asp Gly Met Ala Ser Leu Glu Gly Thr Pro Ala Ser Val Leu Ala
                                       115
                          110
Asp Ala Cys Pro Gly Phe His Asp Val Xaa Val Gln Xaa Ala Leu Phe
                                          130
                    125
Gly Leu Ser Gly Xaa Xaa Leu Trp Leu Lys Thr His Phe Cys Leu Ser
Ile Xaa Leu
<210> 388
<211> 150
<212> PRT
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<222> -55..-1
Met Ala Thr Thr Val Pro Asp Gly Cys Arg Asn Gly Leu Lys Ser Lys
                   -50
                                        -45
Tyr Tyr Arg Leu Cys Asp Lys Ala Glu Ala Trp Gly Ile Val Leu Glu
                                    -30
                -35
Thr Val Ala Thr Ala Gly Val Val Thr Ser Val Ala Phe Met Leu Thr
                                                    -10
                                -15
            -20
Leu Pro Ile Leu Val Cys Lys Val Gln Asp Ser Asn Arg Arg Lys Met
Leu Pro Thr Gln Phe Leu Phe Leu Leu Gly Val Leu Gly Ile Phe Gly
                                        20
                    15
Leu Thr Phe Ala Phe Ile Ile Gly Leu Asp Gly Ser Thr Gly Pro Thr
                                    35
                3.0
Arg Phe Phe Leu Phe Gly Ile Leu Phe Ser Ile Cys Phe Ser Cys Leu
                               50
          45
Leu Ala His Ala Val Ser Leu Thr Lys Leu Val Arg Gly Arg Lys Ala
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Pro Phe Pro Val Gly Asp Ser Gly Ser Gly Arg Gly Leu Gln Pro Ser

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Pro Gly Cys Tyr Arg Tyr
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<211> 236
<212> PRT
<213> Homo sapiens
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<222> -31..-1
<400> 389
Met Leu Ser Lys Gly Leu Lys Arg Lys Arg Glu Glu Glu Glu Lys
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                                        -20
Glu Pro Leu Ala Val Asp Ser Trp Trp Leu Asp Pro Gly His Ala Ala
                                 - 5
               -10
Val Ala Gln Ala Pro Pro Ala Val Ala Ser Ser Ser Leu Phe Asp Leu
                                        15
                            10
Ser Val Leu Lys Leu His His Ser Leu Gln Xaa Ser Xaa Pro Asp Leu
                       25
Arg His Leu Val Leu Val Xaa Asn Thr Leu Arg Arg Ile Gln Ala Ser
                                        45
                   40
Met Ala Pro Ala Ala Ala Leu Pro Pro Val Pro Thr Pro Pro Ala Ala
                                    60
               55
Pro Xaa Val Ala Asp Asn Leu Leu Ala Ser Ser Asp Ala Ala Leu Ser
                                 75
              70
Ala Ser Met Ala Xaa Leu Leu Glu Asp Leu Ser His Ile Glu Gly Leu
                             90
Ser Gln Ala Pro Gln Pro Leu Ala Asp Glu Gly Pro Pro Gly Arg Ser
                                            110
                         105
Ile Gly Gly Xaa Pro Pro Xaa Leu Gly Ala Leu Asp Leu Leu Gly Pro
                                        125
                     120
Ala Thr Gly Cys Leu Leu Asp Asn Gly Leu Glu Gly Leu Phe Glu Asp
                                     140
                  135
Ile Asp Thr Ser Met Tyr Asp Asn Glu Leu Trp Ala Pro Ala Ser Glu
                                 155
               150
Gly Leu Lys Pro Gly Pro Glu Asp Gly Pro Gly Lys Glu Glu Ala Pro
                                               175
                            170
Glu Leu Asp Glu Ala Glu Leu Asp Tyr Leu Met Asp Val Leu Val Gly
      180 185
Thr Gln Ala Leu Glu Arg Pro Pro Gly Pro Gly Arg
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<210> 390
 <211> 149
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 Met Glu Thr Leu Tyr Arg Val Pro Phe Leu Val Leu Glu Cys Pro Asn
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                  -95
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Leu Lys Leu Lys Lys Pro Pro Trp Leu His Met Pro Ser Ala Met Thr
                                -75
             -80
Val Tyr Ala Leu Val Val Val Ser Tyr Phe Leu Ile Thr Gly Gly Ile
                            -60 -55
       -65
Ile Tyr Asp Val Ile Val Glu Pro Pro Ser Val Gly Ser Met Thr Asp
                        -45
Glu His Gly His Gln Arg Pro Val Ala Phe Leu Ala Tyr Arg Val Asn
                     -30
                                      -25
Gly Gln Tyr Ile Met Glu Gly Leu Ala Ser Ser Phe Leu Phe Thr Met
              -15
                                -10
Gly Gly Leu Gly Phe Ile Ile Leu Asp Gly Ser Asn Ala Pro Asn Ile
                                        10
                         5
Pro Lys Leu Asn Arg Phe Leu Leu Leu Phe Ile Gly Phe Val Cys Val
                   20
Leu Xaa Ser Phe Xaa Xaa Ala Arg Val Phe Met Arg Met Lys Leu Pro
                   35
Gly Tyr Leu Met Gly
<210> 391
<211> 69
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -49..-1
<400> 391
Met Pro Phe His Phe Pro Phe Leu Gly Phe Val Cys Leu His Leu His
                                -40
Leu Thr Pro Cys Leu Thr Val Pro Arg Arg Pro Leu Phe Leu Leu
        -30 -25
                                              -20
His Leu Cys Pro His Leu Pro Phe Leu Leu Leu Ser Cys Val Gly
      -15 -10
                                 -5
Xaa Xaa Pro Ser Cys Leu Pro Ser Ser Ser Thr Cys Val Ser Leu His
 1 5
                                 10
Phe Phe Ile Pro Asp
              20
 <210> 392
 <211> 241
 <212> PRT
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 <222> -30..-1
 Met Gly Thr Ala Ser Arg Ser Asn Ile Ala Arg His Leu Gln Thr Asn
                                    -20
               -25
 Leu Ile Leu Phe Cys Val Gly Ala Val Gly Ala Cys Thr Leu Ser Val
                                 - 5
               -10
 Thr Gln Pro Trp Tyr Leu Glu Val Asp Tyr Thr His Glu Ala Val Thr
                                     15
                         10
 Ile Lys Cys Thr Phe Ser Ala Thr Gly Cys Pro Ser Glu Gln Pro Thr
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Cys Leu Trp Phe Arg Tyr Gly Ala His Gln Pro Glu Asn Leu Cys Leu 40 45 Asp Gly Cys Lys Ser Glu Ala Xaa Lys Phe Thr Val Arg Glu Ala Leu 55 60 Lys Glu Asn Gln Val Ser Leu Thr Val Asn Arg Val Thr Ser Asn Asp 75 Ser Ala Ile Tyr Ile Cys Gly Ile Ala Phe Pro Ser Val Pro Glu Ala 90 Arg Ala Lys Gln Thr Gly Gly Gly Thr Thr Leu Val Val Arg Glu Ile 105 110 Lys Leu Leu Ser Lys Glu Leu Arg Ser Phe Leu Thr Ala Leu Val Ser 125 120 Leu Leu Ser Val Tyr Val Thr Gly Val Cys Val Ala Phe Ile Leu Leu 135 140 Ser Lys Ser Lys Ser Asn Pro Leu Arg Asn Lys Glu Ile Lys Glu Asp 155 Ser Gln Lys Lys Lys Ser Ala Arg Arg Ile Phe Gln Glu Ile Ala Gln 170 175 165 Glu Leu Tyr His Lys Arg His Val Glu Thr Asn Gln Gln Ser Glu Lys 190 185 Asp Asn Asn Thr Tyr Glu Asn Arg Arg Val Leu Ser Asn Tyr Glu Arg 200 205 Pro

<210> 393 <211> 47 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -30..-1

<210> 394 <211> 65 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -28..-1 <400> 394

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 -20
 -15

 Leu Gln Trp Ser Leu Leu Val Ala Val Val Ala Gly Ser Val Val Ser -10
 -5
 1

 Tyr Gly Val Thr Arg Val Glu Ser Glu Lys Cys Asn Asn Leu Trp Leu 5
 10
 15
 20

 Phe Leu Glu Thr Gly Gln Leu Pro Lys Asp Arg Ser Thr Asp Gln Xaa

30 35 25

Ser

<210> 395 <211> 73 <212> PRT <213> Homo sapiens

<220> <221> SIGNAL <222> -24..-1

<400> 395

Met Thr Cys Trp Met Leu Pro Pro Ile Ser Phe Leu Ser Tyr Leu Pro -20 -15 -10 Leu Trp Leu Gly Pro Ile Trp Pro Cys Ser Gly Ser Thr Leu Gly Lys - 5 1 Pro Asp Pro Gly Val Trp Pro Ser Leu Phe Arg Pro Trp Asp Ala Ala 10 15 20 Ser Pro Gly Asn Tyr Ala Leu Ser Arg Gly Xaa Asn Xaa Tyr Xaa Xaa 30 Trp Gly Gln Gly Thr His Ser Ser Leu

<210> 396 <211> 60 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -18..-1

<400> 396 Met Pro Cys Pro Thr Trp Thr Cys Leu Lys Ser Phe Pro Ser Pro Thr -15 -10 -5 Ser Ser His Ala Ser Ser Leu His Leu Pro Pro Ser Cys Thr Arg Leu Thr Leu Thr Gln Thr Leu Arg Thr Gly Met His Leu Ser Arg Ala Leu 15 20 25 Gln Gly Thr Leu Thr Arg Leu Gln Ser Thr Pro Ala 35

<210> 397 <211> 192 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -93..-1 <400> 397

Met Ala Glu Leu Gly Leu Asn Glu His His Gln Asn Glu Val Ile Asn -90 -85 Tyr Met Arg Phe Ala Arg Ser Lys Arg Gly Leu Arg Leu Lys Thr Val

-70 Asp Ser Cys Phe Gln Asp Leu Lys Glu Ser Arg Leu Val Glu Asp Thr -50 -60 -55 Phe Thr Ile Asp Glu Val Ser Glu Val Leu Asn Gly Leu Gln Ala Val -40 -35 Val His Ser Glu Val Glu Ser Glu Leu Ile Asn Thr Ala Tyr Thr Asn **-2**5 -20 -15 Val Leu Leu Leu Arg Gln Leu Phe Ala Gln Ala Glu Lys Trp Tyr Leu -10 -5 Lys Leu Gln Thr Asp Ile Ser Glu Leu Glu Asn Arg Glu Leu Leu Glu 10 15 Gln Xaa Ala Glu Phe Glu Lys Ala Xaa Ile Thr Ser Ser Asn Lys Lys 25 Pro Ile Leu Xaa Val Thr Xaa Pro Lys Leu Ala Pro Leu Asn Glu Gly 45 Gly Thr Ala Lys Leu Leu Asn Lys Val Ile Cys Ile Ile Leu Arg Asn .55 60 Gly Lys Ser Leu Ile Leu Ser Cys His Cys Leu Gly Trp Arg Asn Lys 70 75 80 Ser Gly Arg Phe Val Ser Gly Pro Leu Arg Ile Ile Ser Pro Leu Gln

<210> 398 <211> 149 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -72..-1

<400> 398

Met Asn Leu Phe Ile Met Tyr Met Ala Gly Asn Thr Ile Ser Ile Phe -65 -70 Pro Thr Met Met Val Cys Met Met Ala Trp Arg Pro Ile Gln Ala Leu -50 Met Ala Ile Ser Ala Thr Phe Lys Met Leu Glu Ser Ser Ser Gln Lys -35 Phe Leu Gln Gly Leu Val Tyr Leu Ile Gly Asn Leu Met Gly Leu Ala -15 Leu Ala Val Tyr Lys Cys Gln Ser Met Gly Leu Leu Pro Thr His Ala 1 5 -5 Ser Asp Trp Leu Ala Phe Ile Glu Pro Pro Glu Arg Met Glu Ser Val 15 Val Glu Asp Cys Phe Cys Glu His Glu Lys Ala Ala Pro Gly Pro Tyr 30 35 Val Phe Gly Ser Tyr Leu His Pro Ser Leu Ser Pro Val Ala Pro Gln 50 His Thr Leu Lys Leu Ile Thr Tyr Val Lys Lys Asn Gln Lys Thr Leu 65 60 Phe Ser Met Val Gly 75

<210> 399 <211> 73 <212> PRT <213> Homo sapiens

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<222> -20..-1
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       -15 -10
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Cys Phe Asn Pro Met Arg Cys Pro Ala Met Val Ala Tyr Cys Met Thr
                          20
Thr Arg Thr Tyr Tyr Thr Pro Thr Arg Met Lys Val Ser Lys Ser Cys
                     35
Val Pro Arg Cys Phe Glu Xaa Cys Val
               50
<210> 400
<211> 86
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<222> -20..-1
<400> 400
Met Asn Leu His Phe Pro Gln Trp Phe Val His Ser Ser Ala Leu Gly
                                                 - 5
                                   -10
                -15
Leu Val Leu Ala Pro Pro Phe Ser Ser Pro Gly Thr Asp Pro Thr Phe
                                                 10
                             5
Pro Cys Ile Tyr Cys Arg Leu Leu Asn Met Ile Met Thr Arg Leu Ala
                                             25
                          20
Phe Ser Phe Ile Thr Cys Leu Cys Pro Asn Leu Lys Glu Val Cys Leu
                      35
                                         40
Ile Leu Pro Glu Lys Asn Cys Asn Ser Arg His Ala Gly Phe Val Gly
                  50
Pro Xaa Lys Leu Arg Gln
<210> 401
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<222> -21..-1
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45 50 55

<210> 402 <211> 65 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -28..-1

-10 -5 1

Glu Ala Asp Gln Trp Leu Arg Gln Val Trp Gly Glu Val Pro Glu Pro
5 10 15 20

Ser Asp Arg Ser Glu Glu Pro Glu Thr Pro Ala Ala Tyr Arg Ala Arg
25 30 35

Thr

<210> 403
<211> 211
<212> PRT
<213> Homo sapiens
<220>
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<222> -27..-1

<400> 403 Met Leu Leu Ser Ile Thr Thr Ala Tyr Thr Gly Leu Glu Leu Thr -20 -25 Phe Phe Ser Gly Val Tyr Gly Thr Cys Ile Gly Ala Thr Asn Lys Phe -10 -5 Gly Ala Glu Glu Xaa Ser Leu Ile Gly Leu Ser Gly Ile Phe Ile Gly 15 Ile Gly Glu Ile Leu Gly Gly Ser Leu Phe Gly Leu Leu Ser Lys Asn 30 Asn Arg Phe Gly Arg Asn Pro Val Val Leu Leu Gly Ile Leu Val His 4.5 Phe Ile Ala Phe Tyr Leu Ile Phe Leu Asn Met Pro Gly Asp Ala Pro 60 Ile Ala Pro Val Lys Gly Thr Asp Ser Ser Ala Tyr Ile Lys Ser Ser 75 Lys Xaa Phe Ala Ile Leu Cys Xaa Phe Leu Xaa Gly Leu Gly Asn Ser 95 Cys Phe Asn Thr Xaa Leu Leu Xaa Ile Xaa Gly Phe Leu Tyr Ser Glu 110 Xaa Ser Ala Pro Xaa Phe Ala Ile Phe Asn Phe Val Gln Ser Ile Cys 125 130 120 Ala Ala Val Ala Phe Phe Tyr Ser Asn Tyr Leu Leu Leu His Trp Gln 140 145 Leu Leu Val Met Val Ile Phe Gly Phe Xaa Gly Thr Ile Ser Phe Phe 160 Thr Val Glu Trp Glu Xaa Ala Ala Phe Val Xaa Arg Gly Ser Asp Tyr

Arg Ser Ile

<210> 404 <211> 123 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -80..-1 <400> 404 Met Ser Thr Trp Tyr Leu Ala Leu Asn Lys Ser Tyr Lys Asn Lys Asp -70 -75 Ser Val Arg lle Tyr Leu Ser Leu Cys Thr Val Ser Ile Lys Phe Thr -60 -55 Tyr Phe His Asp Ile Gln Thr Asn Cys Leu Thr Thr Trp Lys His Ser -40 -35 -45 Arg Cys Arg Phe Tyr Trp Ala Phe Gly Gly Ser Ile Leu Gln His Ser -20 -25 Val Asp Pro Leu Val Leu Phe Leu Ser Leu Ala Leu Leu Val Thr Pro - 5 -10 -15 Thr Ser Thr Pro Ser Ala Lys Ile Gln Ser Leu Gln Ile Asp Leu Pro 10 1 5 Gly Gly Trp Arg Leu Ala Thr Asp Arg Ile Phe Thr Leu Ser Pro Val 20 25 Pro Met Asp Xaa Pro Leu Ile Leu His Gln Leu 40

<210> 405 <211> 86 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -26..-1

<400> 405 Met Glu Lys Ser Trp Met Leu Trp Asn Phe Val Glu Arg Trp Leu Ile -20 -15 -25 Ala Leu Ala Ser Trp Ser Trp Ala Leu Cys Arg Ile Ser Leu Leu Pro 1 -5 Leu Ile Val Thr Phe His Leu Tyr Gly Gly Ile Ile Leu Leu Leu 15 10 Ile Phe Ile Ser Ile Xaa Gly Ile Leu Tyr Lys Phe Xaa Asp Val Leu 30 35 Leu Tyr Phe Pro Xaa Gln Xaa Ser Ser Ser Arg Leu Tyr Asp Ser His 50 45 40 Ala His Trp Xaa Ser Xaa

<210> 406 <211> 162 <212> PRT <213> Homo sapiens

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 Met Ala Ala Trp Pro Ser Gly Pro Xaa Ala Pro Glu Ala Val Thr
                        -25
                                      -20
 Ala Arg Leu Val Gly Val Leu Trp Phe Val Ser Val Thr Thr Gly Pro
                    -10
                                     -5
  Trp Gly Ala Val Ala Thr Ser Ala Gly Gly Glu Glu Ser Leu Lys Cys
                                10
  Glu Asp Leu Lys Val Gly Gln Tyr Ile Cys Lys Asp Pro Lys Ile Asn
        20
                             25
                                            30
  Asp Ala Thr Gln Glu Pro Val Asn Cys Thr Asn Tyr Thr Ala His Val
                                         45
                         40
  Ser Cys Phe Pro Ala Pro Asn Ile Thr Cys Lys Asp Ser Ser Gly Asn
                                        60
  Glu Thr His Phe Thr Gly Asn Glu Val Gly Phe Phe Lys Pro Ile Ser
                                    75
. Cys Arg Asn Val Asn Gly Tyr Ser Tyr Asn Glu Gln Ser His Val Ser
                                90
  Phe Ser Trp Met Val Gly Ser Arg Ser Ile Leu Pro Trp Ile Pro Cys
                                               110
                            105
  Phe Gly Phe Val Lys Xaa Xaa His Cys Arg Val Xaa Trp Asn Trp Glu
                                            125
  Pro Asn
  130
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<210> 407
<211> 98
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
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<400> 407 Met Ala Ser Leu Leu Cys Cys Gly Pro Lys Leu Ala Ala Cys Gly Ile -30 -35 Val Leu Ser Ala Trp Gly Val Ile Met Leu Ile Met Leu Gly Ile Phe -15 -10 Phe Asn Val His Ser Ala Val Leu Ile Glu Asp Val Pro Phe Thr Glu Lys Asp Phe Glu Asn Gly Pro Gln Asn Ile Tyr Asn Leu Tyr Xaa Gln 25 20 Xaa Ser Tyr Asn Cys Phe Ile Ala Ala Gly Leu. Tyr Leu Leu Leu Gly 35 . 40 Gly Phe Ser Phe Cys Gln Xaa Arg Leu Asn Lys Arg Lys Glu Tyr Met 45 Val Arg 60

<210> 408 <211> 70 <212> PRT <213> Homo sapiens WO 99/31236 -307- PCT/IB98/02122 -

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<220>
<221> SIGNAL
<222> -15..-1
<400> 408
Met Arg Phe Leu Pro Cys Cys Leu Leu Trp Ser Val Phe Asn Pro Glu .
                                     . 1
-15 -10
                       -5
Ser Leu Asn Cys His Tyr Phe Xaa Xaa Glu Xaa Cys Ile Phe Xaa Ser
                    10 15
Leu Gln Tyr Tyr Glu Ile Ser Leu Gln Glu Lys Leu Leu Gly Phe Leu
                              30
. 20
             25
Trp Leu Cys Phe Leu Ser Tyr Phe Phe Arg Ala Val Tyr Phe Leu Ile
          40
Asp Phe Ser Ser Phe Thr
50
                55
<210> 409
<211> 60
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -45..-1
<400> 409
Met His Ser Leu Phe Ile Ala Ser Leu Lys Val Leu Phe Tyr Tyr Ser
                -40
                          -35
Phe Ser Phe Arg Phe Asn Trp Phe Asp Cys Leu Leu His Asn Leu Gly
            -25
                             -20
Glu Asn Phe Leu Ser Leu Leu Ser Lys Ser Cys Ser Ala Asp Pro Ser
   -10
                    - 5
Gly Ser Thr Phe Met Arg Asp Ile Glu Thr Asn Lys
                10
  5
<210> 410
<211> 39
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -22..-1
<400> 410
Met Pro Glu Ala Val Glu Gln Ser Ala His Leu Phe Val Thr Trp Ser
  -20 -15 -10
Ser Gln Arg Ala Leu Ser His Pro Ala Pro Phe Leu Thr Xaa Xaa Lys
                   1
                        5 . 10
-5
Asn Pro Phe Leu Trp Lys Leu
            15
```

<210> 411 <211> 51 <212> PRT WO 99/31236 -308- PCT/IB98/02122

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<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 411
Met Ala Phe Gln Ser Leu Leu Glu Met Lys Phe Phe Leu Cys Ala Ala
       -20
                           -15
                                                  -10
Phe Pro Leu Gly Ala Gly Val Lys Met Phe His Tyr Leu Gly Pro Gly
Lys Pro Leu Xaa Gln Ala Ser Pro Ser Pro His Pro His Arg Xaa Arg
10
                   15
                                    20
Ile Trp Pro
<210> 412
<211> 95
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -48..-1
<400> 412
Met Ala Ser Ser His Trp Asn Glu Thr Thr Thr Ser Val Tyr Gln Tyr
                               -40
Leu Gly Phe Gln Val Gln Lys Ile Tyr Pro Phe His Asp Asn Trp Asn
       -30
                           -25
                                              -20
Thr Ala Cys Phe Val Ile Leu Leu Phe Ile Phe Thr Val Val Ser
                      -10
  -15
                                        -5
Leu Val Val Leu Ala Phe Leu Tyr Glu Val Leu Xaa Xaa Cys Cys
                                  10
Val Lys Asn Lys Thr Val Lys Asp Leu Lys Ser Glu Pro Asn Pro Leu
                             25
          20
Xaa Xaa Met Met Asp Asn Ile Arg Lys Arg Glu Thr Glu Val Val
                           40
<210> 413
<211> 60
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -32..-1
<400> 413
Met Asp Glu Tyr Ser Trp Trp Cys His Val Leu Glu Val Val Lys Gly
                        -25
Gln Met Phe Thr Phe Ile Asn Ile Thr Leu Trp Leu Gly Ser Leu Cys
                       -10
                                          - 5
Gln Arg Phe Phe Tyr Ala Ser Gly Thr Tyr Phe Leu Ile Tyr Ile Ser
            5
                               10
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Thr Val Thr Pro Ser Trp Arg Leu Cys Leu Val Ser

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<210> 414
<211> 170
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -79..-1
<400> 414
Met Glu Asp Pro Asn Pro Glu Glu Asn Met Lys Gln Gln Asp Ser Pro
      <del>-</del>75 -70 -65
Lys Glu Arg Ser Pro Gln Ser Pro Gly Gly Asn Ile Cys His Leu Gly
                -55
        -60
Ala Pro Lys Cys Thr Arg Cys Leu Ile Thr Phe Ala Asp Ser Lys Phe
      -45 -40
                                       -35
Gln Glu Arg His Met Lys Arg Glu His Pro Ala Asp Phe Val Ala Gln
                -25
                          ~20
Lys Leu Gln Gly Val Leu Phe Ile Cys Phe Thr Cys Ala Arg Ser Phe
-15
             -10
                       -5
Pro Ser Ser Lys Ala Xaa Xaa Thr His Gln Arg Ser His Gly Pro Xaa
   5
                       10
Ala Lys Pro Thr Leu Pro Val Ala Thr Thr Thr Ala Gln Pro Thr Phe
                    25
Pro Cys Pro Asp Cys Gly Lys Thr Phe Gly Gln Ala Val Ser Leu Xaa
                  40
Arg His Xaa Gln Xaa His Glu Val Arg Ala Pro Pro Gly Thr Phe Ala
50 55 60 .
Cys Thr Xaa Cys Gly Gln Asp Phe Ala Gln Glu Xaa Gly Leu His Gln
           70
                      75
His Tyr Ile Arg His Ala Arg Gly Gly Leu
```

-55

-25 -20

-40

10

25

Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp Ile

Ile Leu Ala Ser Asp Val Phe Phe Glu Pro Glu Xaa Phe Glu Asp Ile

Leu Ala Thr Ile Tyr Phe Leu Met His Lys Asn Pro Lys Val Gln Leu

<210> 415 <211> 190 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -82..-1 <400> 415 Met Tyr Val Trp Pro Cys Ala Val Val Leu Ala Gln Tyr Leu Trp Phe -80 -75 -70 His Arg Arg Ser Leu Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala Gly -60 Val Ser Leu Pro Gly Ile Leu Ala Ala Lys Cys Gly Ala Glu Val Ile -50 -45 Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg Gln -30 Ser Cys Gln Met Asn Asn Leu Pro His Leu Gln Val Val Gly Leu Thr -15 -10 -5

20

WO 99/31236 -310- PCT/IB98/02122 -

<210> 416 <211> 114 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -60..-1 <400> 416 Met Met Ala Ala Val Pro Pro Gly Leu Glu Pro Trp Asn Arg Val Arg -55 -50 Ile Pro Lys Ala Gly Asn Arg Ser Ala Val Thr Val Gln Asn Pro Gly -40 -35 -30 Ala Ala Leu Asp Leu Cys Ile Ala Ala Val Ile Lys Glu Cys His Leu -20 Val Ile Leu Ser Leu Lys Ser Gln Thr Leu Asp Ala Glu Thr Asp Val -10 - 5 Leu Cys Ala Val Leu Tyr Ser Asn His Asn Arg Met Gly Arg His Lys 10 15 Pro His Leu Ala Leu Lys Gln Val Glu Gln Cys Leu Lys Arg Leu Lys 30

Asn Met Asn Leu Glu Gly Ser Ile Gln Asp Leu Phe Glu Leu Phe Ser

<210> 417 <211> 161 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -108..-1

Ser Lys

<400> 417 Met Thr Ser Gly Gln Ala Arg Ala Ser Xaa Gln Ser Pro Gln Ala Leu -100 -105 Glu Asp Ser Gly Pro Val Asn Ile Ser Val Ser Ile Thr Leu Thr Leu -85 -80 Asp Pro Leu Lys Pro Phe Gly Gly Tyr Ser Arg Asn Val Thr His Leu -70 Tyr Ser Thr Ile Leu Gly His Gln Ile Gly Leu Ser Gly Arg Glu Ala -55 -50 His Glu Glu Ile Asn Ile Thr Phe Thr Leu Pro Thr Ala Trp Ser Ser -40 -35 . Asp Asp Cys Ala Leu His Gly His Cys Glu Gln Val Val Phe Thr Ala -20 -15 Cys Met Thr Leu Thr Ala Ser Pro Gly Val Phe Pro Ser Leu Tyr Ser

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-10
His Arg Thr Val Phe Leu Thr Arg Thr Ala Thr Pro Arg Ser Gly Thr 5
10
Arg Ser Ser Gln Leu Pro Glu Met Pro Thr Gln Asn Thr Pro Lys Ile
25
Thr Ile Leu Ser Gly Val Ile Arg Gly Pro Leu Glu Lys Ser Ile Met
40
45
Leu
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<212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 <400> 418 Met Leu Gly Gly Asp His Arg Ala Leu Leu Leu Lys Ile Trp Leu Leu -15 -10 Gln Arg Pro Glu Ser Gln Glu Gly Leu Leu Pro Gly Arg Leu Val Val Met Glu Arg Arg Val Lys Asn Asp Leu Met Ser Phe Leu Ser Thr Val 15 20 Leu Leu Ser Phe His Ser Ser Asn Ala Arg Val Ser His Cys Glu Pro 30 35 Leu Arg Met 45

<210> 419 <211> 332 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -32..-1

<400> 419

<210> 418 <211> 67

Met Ile Xaa Leu Arg Asp Thr Ala Ala Ser Leu Arg Leu Glu Arg Asp -30 -25 -20 Thr Arg Gln Leu Pro Leu Leu Thr Ser Ala Leu His Gly Leu Gln Gln -10 - 5 Gln His Pro Ala Phe Ser Gly Val Ala Arg Leu Ala Lys Arg Trp Val Arg Ala Gln Leu Leu Gly Glu Gly Phe Ala Asp Glu Ser Leu Asp Leu 25 Val Ala Ala Leu Phe Leu His Pro Glu Pro Phe Thr Pro Pro Ser 40 45 Ser Pro Gln Val Gly Phe Leu Arg Phe Leu Phe Leu Val Ser Thr Phe Asp Trp Lys Asn Asn Pro Leu Phe Val Asn Leu Asn Asn Glu Leu Thr 70 75 Val Glu Glu Gln Val Glu Ile Arg Ser Gly Phe Leu Ala Ala Arg Ala 85 90 Gln Leu Pro Val Met Val Ile Val Thr Pro Gln Xaa Arg Lys Asn Ser 100 105

Val Trp Thr Gln Asp Gly Pro Ser Ala Gln Ile Leu Gln Gln Leu Val 120 Val Leu Ala Ala Glu Xaa Leu Pro Met Leu Xaa Xaa Gln Leu Met Asp 135 140 Pro Arg Gly Pro Gly Asp Ile Arg Thr Xaa Phe Arg Pro Pro Leu Asp 150 155 Ile Tyr Asp Val Leu Ile Arg Leu Ser Pro Arg His Ile Pro Arg His 165 170 . 175 Arg Gln Ala Val Asp Ser Pro Ala Ala Ser Phe Cys Arg Gly Leu Leu 185 190 Ser Gln Pro Gly Pro Ser Ser Leu Met Pro Val Leu Gly Xaa Asp Pro 200 205 Pro Gln Leu Tyr Leu Thr Gln Leu Xaa Glu Ala Phe Gly Asp Leu Ala 215 220 Leu Phe Phe Tyr Asp Gln His Gly Glu Val Ile Gly Val Leu Trp 230 235 Lys Pro Thr Ser Phe Gln Pro Gln Pro Phe Lys Ala Ser Ser Thr Lys 245 250 Gly Arg Met Val Met Ser Arg Gly Glu Leu Val Met Val Pro Asn 265 Val Glu Ala Ile Leu Glu Asp Phe Ala Val Leu Gly Glu Gly Leu Val 275 280 Gln Thr Val Glu Ala Arg Ser Glu Arg Trp Thr Val 290 295

Met Gly Gly Ile Trp Asn Ala Leu Ser Met Ser Ser Phe Ser Phe His
-15 -16 -10 -10 -5

Ser Ser Ser Cys Ser Ala Leu Ser Ala Lys Ser Leu Leu Ser Arg His
1 5 5 10

His Ile Leu Gln Gln Phe Leu Val Arg Lys Ser Val Pro Leu Glu Asn
15 20 25

Ala Ser Leu Pro Phe Pro His Leu Gly Ser Ser Leu Phe Lys Ile Val
30 35 40 45

<210> 421 <211> 57 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -30..-1

-10 -5 1

Arg Val Tyr His Tyr Phe Gln Trp Arg Arg Ala Gln Arg Gln Ala Ala
5 10 15

Glu Glu Gln Lys Xaa Ser Gly Ile Met
20 25

<210> 422 <211> 85 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -17..-1 <400> 422 Met Lys Lys Val Leu Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val -10 Gly Phe Pro Val Ser Gln Asp Gln Glu Arg Glu Lys Arg Ser Ile Ser 10 Asp Ser Asp Glu Leu Ala Ser Gly Xaa Phe Val Phe Pro Tyr Pro Tyr 20 25 Pro Phe Arg Pro Leu Pro Pro Ile Pro Phe Pro Arg Phe Pro Trp Phe 4.5

35 40 45
Arg Arg Asn Phe Pro Ile Pro Ile Pro Glu Ser Ala Pro Thr Thr Pro
50 55 60

Leu Pro Ser Glu Lys

65

<210> 423 <211> 85 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -17..-1 <400> 423

Leu Pro Ser Glu Lys

<210> 424 <211> 69 <212> PRT <213> Homo sapiens

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<220>
<221> SIGNAL
<222> -29..-1
<400> 424
Met Thr Cys Arg Gly Ser Cys Ser Tyr Ala Thr Arg Arg Ser Pro Ser
                                -20 ·
              -25
Glu Leu Ser Leu Leu Pro Ser Ser Leu Trp Val Leu Ala Thr Ser Ser
                           - 5
          -10
Pro Thr Ile Thr Ile Ala Leu Ala Met Ala Ala Gly Asn Leu Cys Pro
                     10
                                      15
Leu Pro Ser Ser Xaa Arg Xaa Lys Arg Arg Trp Cys Gln Ala Xaa Gln
                              30
Gln Xaa Ala Leu Leu
            40
<210> 425
<211> 122
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -56..-1
<400> 425
Met Val Pro Trp Pro Arg Gly Lys Val Lys Thr Ala Pro Ile Pro Ile
                    -50
                              -45
Ser Arg Phe Pro Phe Leu Pro Thr His Asp Pro Pro Thr Pro Ala His
                                    -30
               -35
Trp Ser Pro Ala Ser His Gln Gln Phe Lys His Xaa Ser Pro Leu Leu
                               -15
              -20
Thr Leu Ala Leu Leu Gly Gln Cys Ser Leu Phe Xaa Asn Leu Arg Lys
                              1
           - 5
Lys Leu Ala Gly Gln Lys Ala Lys Leu Pro Ser Phe Ser Ser Leu
                                         20
                      15
Pro Leu Thr Leu Trp Pro Leu Thr Pro Gln Phe Ala Glu Leu Thr Thr
                                  35
                  30
Val Ala Gln Lys Lys Leu Arg Trp Ser Gly Thr Leu Gly Trp Gly Pro
              45
Val Pro Ser Trp Val Gln Phe Phe Leu Gly
           60
<210> 426
<211> 41
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -30..-1
<400> 426
Met Ala Cys Glu Thr His Gly Val Leu Val Pro Ala His Leu Ser Gly
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Leu Ile Thr Cys Leu Leu Ala Phe Trp Val Pro Ala Ser Cys Ile Gln

-5

-30 -25

-10

-20 -15

Arg Cys Ser Gly Ser Pro Leu Pro Leu 5

<210> 427
<211> 50
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -36..-1
<400> 427

Leu Ile

<210> 428 <211> 136 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -18..-1

<400> 428

Met Asp Ser Leu Arg Lys Met Leu Ile Ser Val Ala Met Leu Gly Ala -15 -10 Xaa Ala Gly Val Gly Tyr Ala Leu Leu Val Ile Val Thr Pro Gly Glu 10 Arg Arg Lys Gln Glu Met Leu Lys Glu Met Pro Leu Gln Asp Pro Arg 20 25 Ser Arg Glu Glu Ala Ala Arg Thr Gln Gln Leu Leu Ala Thr Leu 35 40 Gln Glu Ala Ala Thr Thr Gln Glu Asn Val Ala Trp Arg Lys Asn Trp 55 50 Met Val Gly Gly Gly Gly Ala Thr Gly Xaa His Arg Glu Thr Gly 70 75 Leu Ala Ser Val Gly Ala Gly Pro Trp Leu Gly Arg Arg Asn Pro Arg 85 Gln Leu Ser Pro Ser Trp Ala Xaa Arg Lys Ile Arg Xaa Glu Asn Xaa 100 105 Met Pro Gly Leu Ser Gly Val Leu

<210> 429 <211> 194 <212> PRT <213> Homo sapiens

<220>

115

-55

-20

-40

<222> -65..-1 <400> 429 Met Gln Asp Ala Pro Leu Ser Cys Leu Ser Pro Thr Lys Trp Ser Ser -60 Val Ser Ser Ala Asp Ser Thr Glu Lys Ser Ala Ser Ala Ala Gly Thr -45 Arg Asn Leu Pro Phe Gln Phe Cys Leu Arg Gln Ala Leu Arg Met Lys -25 Ala Ala Gly Ile Leu Thr Leu Ile Gly Cys Leu Val Thr Gly Val Glu -10

- 5 Ser Lys Ile Tyr Thr Arg Cys Lys Leu Ala Lys Ile Phe Ser Arg Ala 10

Gly Leu Asp Asn Xaa Arg Gly Phe Ser Leu Gly Asn Trp Ile Cys Met 25 20

Ala Tyr Tyr Glu Ser Gly Tyr Asn Thr Thr Ala Gln Thr Val Leu Asp 40

Asp Gly Ser Ile Asp Tyr Gly Ile Phe Gln Ile Asn Ser Phe Ala Trp 55 60

Cys Arg Arg Gly Lys Leu Lys Glu Asn Asn His Cys His Val Ala Cys 70 75

Ser Ala Leu Xaa Thr Asp Asp Leu Thr Asp Ala Ile Ile Cys Ala Xaa 85 90 Lys Ile Val Lys Glu Thr Gln Gly Met Asn Tyr Trp Gln Gly Trp Lys

105 100 Lys His Cys Glu Gly Arg Asp Leu Ser Xaa Trp Lys Lys Gly Cys Glu

120

Val Ser

<210> 430 <211> 141

<221> SIGNAL

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -69..-1

<400> 430

Met Thr Ser Gln Pro Val Pro Asn Glu Thr Ile Ile Val Leu Pro Ser -65 -60 Asn Val Ile Asn Phe Ser Gln Ala Glu Lys Pro Glu Pro Thr Asn Gln -45

Gly Gln Asp Ser Leu Lys Lys His Leu His Ala Glu Ile Lys Val Ile -30 -25

Gly Thr Ile Gln Ile Leu Cys Gly Met Met Val Leu Ser Leu Gly Ile -15 -10

Ile Leu Ala Ser Ala Ser Phe Ser Pro Asn Phe Thr Gln Val Thr Ser 1

Thr Leu Leu Asn Ser Ala Tyr Pro Phe Ile Gly Pro Phe Phe Val Xaa

20 Lys Xaa Ser Glu Glu Gly Arg Met Gly Gln Xaa Gly Glu Glu Xaa Xaa

35 Asn Ser Leu Asn Phe Pro Xaa Ala Ser Leu Leu Xaa Leu Ile Cys Gln

50 Xaa Gln Gly Phe Asn Gly Glu Ser Cys Ser Pro Val Gly WO 99/31236 -317- PCT/IB98/02122 -

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<210> 431
<211> 248
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -69..-1
<400> 431
Met Thr Ser Gln Pro Val Pro Asn Glu Thr Ile Ile Val Leu Pro Ser
              -65
                                 -60
Asn Val Ile Asn Phe Ser Gln Ala Glu Lys Pro Glu Pro Thr Asn Gln
          -50
                              -45
Gly Gln Asp Ser Leu Lys Lys His Leu His Ala Glu Xaa Lys Val Ile
                               -25
    -35 <
                         -30
Gly Thr Ile Gln Ile Leu Cys Gly Met Met Val Leu Ser Leu Gly Ile
                      -15
                                       -10
Ile Leu Ala Ser Ala Ser Phe Ser Pro Asn Phe Thr Gln Val Thr Ser
                              5
Thr Leu Leu Asn Ser Ala Tyr Pro Phe Ile Gly Pro Phe Phe Ile
          15
                              20
Ile Ser Gly Ser Leu Ser Ile Ala Thr Lys Lys Arg Leu Thr Asn Leu
    30
                                             40
                         35
Leu Val His Thr Thr Leu Val Gly Ser Ile Leu Ser Ala Leu Ser Ala
                      50
                                         55
Leu Val Gly Phe Ile Xaa Leu Ser Val Lys Gln Ala Thr Leu Asn Pro
                                     70 -
                  65
Ala Ser Leu Xaa Cys Glu Leu Xaa Lys Asn Asn Ile Pro Thr Xaa Xaa
                                  85
                                                     90
Tyr Val Xaa Tyr Phe Tyr His Asp Ser Leu Tyr Thr Thr Asp Xaa Tyr
          95
                              100
                                                105
Thr Ala Lys Ala Xaa Leu Ala Gly Thr Leu Ser Leu Met Leu Ile Cys
      110
                         115
                                            120
Thr Leu Leu Glu Phe Cys Xaa Xaa Val Leu Thr Ala Val Leu Arg Trp
                     130
                                         135
Lys Gln Ala Tyr Ser Asp Phe Pro Gly Ser Val Leu Phe Leu Pro Xaa
                  145 150
Ser Tyr Ile Gly Asn Ser Gly Met Ser Ser Lys Met Thr His Asp Cys
              160
                                 165
Gly Tyr Glu Glu Leu Leu Thr Ser
          175
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Phe

<210> 433

<211> 86 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -14..-1 <400> 433 Met Val Ala Leu Asn Leu Ile Leu Val Pro Cys Cys Ala Ala Trp Cys -10 -5 Asp Pro Arg Arg Ile His Ser Gln Asp Asp Val Leu Arg Ser Ser Ala 10 15 Ala Asp Thr Gly Ser Ala Met Gln Arg Arg Glu Ala Trp Ala Gly Trp 20 25 30 . Arg Arg Ser Gln Pro Phe Ser Val Gly Leu Pro Ser Ala Glu Arg Leu 45 40 Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg Ser Leu Val Gly Glu Gly 60 55 His Arg Ile Cys Asp Leu 70

<210> 434 <211> 144 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -58..-1

<400> 434

Met Thr Arg Leu Cys Leu Pro Arg Pro Glu Ala Arg Glu Asp Pro Ile -50 Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser Pro -35 -30 Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu Leu -15 -20 -25 Asp Ser Val Leu Trp Leu Gly Ala Leu Gly Leu Thr Ile Gln Ala Val -10 -5 ٦ Phe Ser Thr Thr Gly Pro Ala Leu Leu Leu Leu Val Ser Phe Leu 10 15 20 Thr Phe Asp Leu Leu His Arg Pro Ala Val Thr Leu Cys His Ser Ala 30 35 Asn Phe Ser Pro Gly Ala Arg Val Arg Gly Pro Val Lys Val Leu Asp 45 50 Ser Arg Arg Leu Tyr Ser Cys Lys Trp Val Gln Ser Gln Asp Asn Leu 60 65 Ala Ser Arg Lys His Cys Cys Cys Cys Ser Trp Gly Trp Ala Arg Ser 80 75

<210> 435 <211> 121 WO 99/31236 -319- PCT/IB98/02122 -

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<212> PRT
  <213> Homo sapiens
  <220>
  <221> SIGNAL
  <222> -16..-1
  <400> 435
  Met Glu Arg Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala
                         -10
                                          - 5
  Ser Ala Gly Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln
                                     10
  Cys Phe Lys Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser
             20
                                 25
                                                     30
  Pro Leu Asp Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Ser
        35
                                                45
                             40
  Glu Ser Pro Pro Gly Arg Gly Xaa Val Pro Xaa Ala Gly Glu Xaa Pro
                         55
                                            60
  Val Pro Pro Pro Leu Xaa Asp Leu Xaa Met Thr Pro Arg Xaa Xaa Arg
                     70
                                         75
. Ala Trp Gly Pro Val Gly Pro Lys Val Pro Pro Ala Val Ser Pro Ala
                 85
                                 90
  Leu Gly Ser Gly Glu His Pro Xaa Xaa
             100
  <210> 436
  <211> 162
  <212> PRT
  <213> Homo sapiens
  <220>
  <221> SIGNAL
  <222> -16..-1
  <400> 436
  Met Glu Arg Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala
                         -10
  Ser Ala Gly Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln
                 5
                                    10
  Cys Phe Lys Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser
             20
                                25
  Pro Leu Asp Gln Val Cys Ile Ser Asn Glu Val Val Ser Phe Lys
         35
                             40
                                                4.5
  Trp Ser Val Arg Val Leu Leu Ser Lys Arg Cys Ala Pro Arg Cys Pro
                         55
                                             60
  Asn Asp Asn Met Xaa Phe Glu Trp Ser Pro Ala Pro Met Val Gln Gly
                     70
                                         75
  Val Ile Thr Arg Arg Cys Cys Ser Trp Ala Leu Cys Asn Arg Ala Leu
                 85
                                     90
  Thr Pro Gln Glu Gly Arg Trp Ala Leu Xaa Gly Gly Leu Leu Gln
                                 105
  Asp Pro Ser Arg Gly Xaa Lys Thr Trp Val Arg Pro Gln Leu Gly Leu
                             120
                                                125
  Pro Leu Cys Leu Pro Xaa Ser Asn Pro Leu Cys Pro Xaa Glu Thr Gln
    130
                        135
```

Glu Gly 145

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<210> 437
  <211> 110
  <212> PRT
  <213> Homo sapiens
  <220>
  <221> SIGNAL
  <222> -20..-1
  <400> 437
  Met Xaa Leu Met Val Leu Val Phe Thr Ile Gly Leu Thr Leu Leu Leu
               -15
                                         -10
  Gly Xaa Gln Ala Met Pro Ala Asn Arg Leu Ser Cys Tyr Arg Lys Ile
                 1
  Leu Lys Asp His Asn Cys His Asn Leu Pro Glu Gly Val Ala Asp Leu
                             20
  Thr Gln Ile Asp Val Asn Val Gln Asp His Phe Trp Asp Gly Lys Gly
                         35
                                             40
  Cys Glu Met Ile Cys Tyr Cys Asn Phe Lys Arg Ile Ala Leu Leu Pro
  45
                     50
                                        55
. Lys Arg Arg Phe Leu Trp Thr Lys Asp Leu Phe Arg Asp Ser Leu Gln
                                     70
                65
  Gln Ser Met Arg Ile Phe Met Tyr Ser Gly Glu His His Ser
                                 85
  <210> 438
 <211> 71
  <212> PRT
  <213> Homo sapiens
  <220>
  <221> SIGNAL
  <222> -15..-1
  <400> 438
  Met Lys Leu Leu Thr His Asn Leu Leu Ser Ser His Val Arg Gly Val
                  -10
                                         - 5
  Gly Ser Arg Gly Phe Pro Leu Arg Leu Gln Ala Thr Glu Val Arg Ile
                                10
  Cys Pro Val Glu Phe Asn Pro Asn Phe Val Ala Arg Met Ile Pro Lys
                            25
  Val Glu Trp Ser Ala Phe Leu Glu Ala Xaa Asp Asn Leu Arg Leu Ile
                       40
  Gln Val Pro Arg Arg Ala Gly
                     55
  <210> 439
  <211> 99
  <212> PRT
  <213> Homo sapiens
  <220>
  <221> SIGNAL
  <222> -24..-1
  <400> 439
  Met Lys Ser Ala Lys Leu Gly Phe Leu Leu Arg Phe Phe Ile Phe Cys
```

-15

-20

 Ser
 Leu
 Asn
 Thr
 Leu
 Leu
 Leu
 Gly
 Gly
 Val
 Asn
 Lys
 Ile
 Ala
 Glu
 Lys

 Ile
 Cys
 Gly
 Asp
 Leu
 Lys
 Asp
 Pro
 Cys
 Lys
 Leu
 Asp
 Met
 Asn
 Phe
 Gly

 Ser
 Cys
 Tyr
 Glu
 Val
 His
 Phe
 Arg
 Tyr
 Phe
 Tyr
 Asn
 Arg
 Thr
 Ser
 Lys
 Asn
 Gly
 Asn
 A

<210> 440
<211> 169
<212> PRT
<213> Homo sapiens

<220>
<221> SIGNAL
<222> -25..-1

<400> 440 Met Arg Lys Pro Ala Ala Gly Phe Leu Pro Ser Leu Leu Lys Val Leu -20 -15 Leu Leu Pro Leu Ala Pro Ala Ala Ala Gln Asp Ser Thr Gln Ala Ser - 5 Thr Pro Gly Ser Pro Leu Ser Pro Thr Glu Tyr Gln Arg Phe Phe Ala 10 Leu Leu Thr Pro Thr Trp Lys Ala Glu Thr Thr Cys Arg Leu Arg Ala 30 Thr His Gly Cys Arg Asn Pro Thr Leu Val Gln Leu Asp Gln Tyr Glu 45 50 Asn His Gly Leu Val Pro Asp Gly Ala Val Cys Ser Asn Leu Pro Tyr 65 Ala Ser Trp Phe Glu Ser Phe Cys Gln Phe Thr His Tyr Arg Cys Ser 80 Asn His Val Tyr Tyr Ala Lys Arg Val Leu Cys Ser Gln Pro Val Ser 95 100 Ile Leu Ser Pro Asn Thr Leu Lys Glu Ile Glu Xaa Ser Ala Glu Val 110 115 Ser Pro Thr Thr Asp Asp Leu Pro His Leu Thr Pro Leu His Ser Asp 125 130 Arg Thr Pro Asp Leu Pro Ala Leu Ala

<210> 441 <211> 167 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -76..-1

140

Met Gly Asp Tyr Leu Leu Arg Gly Tyr Arg Met Leu Gly Glu Thr Cys
-75
-70
-65

Ala Asp Cys Gly Thr Ile Leu Leu Gln Asp Lys Gln Arg Lys Ile Tyr -55 -50 Cys Val Ala Cys Gln Glu Leu Asp Ser Asp Val Asp Lys Asp Asn Pro -40 -35 Ala Leu Asn Ala Gln Ala Ala Leu Ser Gln Ala Arg Glu His Gln Leu -25 -20 Ala Ser Ala Ser Glu Leu Pro Leu Gly Ser Arg Pro Ala Pro Gln Pro -5 Pro Val Pro Arg Pro Glu His Cys Glu Gly Ala Ala Gly Leu Lys 10 15 Ala Ala Gln Gly Pro Pro Ala Pro Ala Val Pro Pro Asn Thr Xaa Val 35 25 30 Met Ala Cys Thr Gln Thr Ala Leu Leu Gln Lys Leu Thr Trp Ala Ser 40 45 Ala Glu Leu Gly Ser Xaa Thr Ser Xaa Gly Lys Xaa Ala Ser Ser Cys 60 Val Ala Leu Ser Ala His Val Arg Arg Pro Cys Ala Ala Cys Ser Ser 75 80 Tyr Ser Thr Lys Arg Ser Pro 85 90

<210> 442 <211> 70 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1

Met Ile Leu Cys Phe Leu Leu Pro His His Arg Leu Gln Glu Ala Arg
-15
-10
-5
1
Gln Ile Gln Val Leu Lys Met Leu Pro Arg Glu Lys Leu Arg Arg Arg
5
10
Glu Glu Arg Lys Gln Ile Asn Gly Lys Lys Xaa Arg Thr Lys Tyr Glu
20
25
25
30
Thr Pro Arg Lys Xaa Xaa Gly Lys Lys Gly Gly Asn Xaa Xaa Xaa
35
Xaa Leu Ser Lys Arg Asp
50

<210> 443 <211> 381 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -33..-1 <400> 443

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Lys Met Ala Thr Val Lys Ser Glu Leu Ile Glu Arg Phe Thr Ser Glu Lys Pro Val His His Ser Lys Val Ser Ile Ile Gly Thr Gly Ser Val Gly Met Ala Cys Ala Ile Ser Ile Leu Leu Lys Gly Leu Ser Asp Glu Leu Ala Leu Val Asp Leu Asp Glu Xaa Lys Leu Lys Gly Glu Thr Met Asp Leu Gln His Gly Ser Pro Phe Thr Lys Met Pro Asn Ile Val Cys Ser Lys Xaa Tyr Phe Val Thr Ala Asn Ser Asn Leu Val Ile Ile Thr Ala Gly Ala Arg Gln Xaa Lys Gly Glu Thr Arg Leu Asn Leu Xaa Gln Arg Asn Val Ala Ile Phe Lys Leu Met Ile Ser Ser Ile Val Gln Tyr Ser Pro His Cys Lys Leu Ile Ile Val Ser Asn Pro Val Asp Ile Leu Thr Tyr Val Ala Trp Lys Leu Ser Ala Phe Pro Lys Asn Arg Ile Ile . Gly Ser Gly Cys Asn Leu Ile Xaa Ala Arg Phe Arg Phe Leu Ile Gly Gln Lys Leu Gly Ile His Ser Glu Ser Cys His Gly Trp Ile Leu Gly Glu His Gly Asp Ser Ser Val Pro Val Trp Ser Gly Val Asn Ile Ala Gly Val Pro Leu Lys Asp Leu Asn Ser Asp Ile Gly Thr Asp Lys Asp Pro Glu Gln Trp Lys Asn Val His Lys Glu Val Thr Ala Thr Ala Tyr Glu Ile Ile Lys Met Lys Gly Tyr Thr Ser Trp Ala Ile Gly Leu Ser Val Ala Asp Leu Thr Glu Ser Ile Leu Lys Asn Leu Arg Arg Ile His Pro Val Ser Thr Ile Thr Lys Gly Leu Tyr Gly Ile Xaa Glu Glu Val Phe Leu Ser Ile Pro Cys Ile Leu Gly Glu Asn Gly Ile Thr Asn Leu Ile Lys Ile Lys Leu Thr Pro Glu Glu Glu Ala His Leu Lys Lys Ser Ala Lys Thr Leu Trp Glu Ile Gln Asn Lys Leu Lys Leu

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<210> 445
<211> 50
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 445
Met Val Leu Thr Thr Leu Pro Leu Pro Ser Ala Asn Ser Pro Val Asn
                                 -25
    -35
                  -30
Met Pro Thr Thr Gly Pro Asn Ser Leu Ser Tyr Ala Ser Ser Ala Leu
                     -15
                                     -10
Ser Pro Cys Leu Thr Ala Pro Lys Ser Pro Arg Leu Ala Met Met Pro
                 1
                              5
Asp Asn
<210> 446
<211>.51
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 446
Met Thr Pro Trp Cys Leu Ala Cys Leu Gly Arg Arg Pro Leu Ala Ser
               -20
                               -15
Leu Gln Trp Ser Leu Thr Leu Ala Trp Cys Gly Ser Gly Ser His Trp
-10
                  - 5
Thr Glu Arg Pro Xaa Gln Xaa Ser Pro Trp Xaa Ser Leu Ser Ala Thr
          10
Thr Arg Gly
      25
<210> 447
<211> 242
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -30..-1
<400> 447
Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arg Arg His Leu Leu Val
               -25
                                    -20
Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Pro
              -10
                                 -5
Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu
                         10
Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys Gly Asn Leu
                      25
Leu Arg Gly Ile Asp Ser Leu Phe Ser Ala Pro Met Asp Phe Arg Gly
```

```
40
Leu Pro Gly Asn Tyr His Lys Glu Glu Asn Gln Glu His Gln Leu Gly
           55
                                60
Asn Asn Thr Leu Ser Ser His Leu Gln Ile Asp Lys Met Thr Asp Asn
                            75
Lys Thr Gly Glu Val Leu Ile Ser Glu Asn Val Val Ala Ser Ile Gln
                        90
Pro Xaa Glu Gly Xaa Phe Glu Gly Asp Leu Lys Val Pro Arg Met Glu
               105
                                       110
Glu Lys Glu Ala Leu Val Pro Xaa Gln Lys Ala Thr Asp Ser Phe His
               120
                                   125
Thr Glu Leu His Pro Arg Val Ala Phe Trp Ile Ile Lys Leu Pro Arg
              135
                                 140
Arg Arg Ser His Gln Asp Ala Leu Glu Gly Gly His Trp Leu Xaa Glu
          150
                             155
Lys Arg His Arg Leu Gln Ala Ile Arg Asp Gly Leu Arg Lys Gly Thr
       165 \ 170
                                  175
His Lys Asp Xaa Leu Xaa Xaa Gly Thr Glu Ser Ser His Ser Arg
                     185
                                     190
Leu Ser Pro Arg Lys Xaa His Leu Leu Tyr Ile Leu Xaa Pro Ser Arg
               200
Gln Leu
```

<210> 448 <211> 154 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -60..-1

<400> 448

Met Gly Ser Lys Cys Cys Lys Gly Gly Pro Asp Glu Asp Ala Val Glu -55 -50 Arg Gln Arg Arg Gln Lys Leu Leu Leu Ala Gln Leu His His Arg Lys -35 Arg Val Lys Ala Ala Gly Gln Ile Gln Ala Trp Trp Arg Gly Val Leu -25 -20 -15 Val Arg Arg Thr Leu Leu Val Ala Ala Leu Arg Ala Trp Met Ile Gln -10 -5 · Cys Trp Trp Arg Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln 10 15 Ala Leu Leu Gly Val Tyr Val Ile Gln Glu Gln Ala Ala Val Lys Leu 30 Gln Ser Cys Ile Arg Met Trp Gln Cys Arg Gln Cys Tyr Arg Gln Met 50 45 Cys Asn Ala Leu Cys Leu Phe Gln Val Pro Lys Ser Ser Leu Ala Phe 60 Gln Thr Asp Gly Phe Leu Gln Val Gln Tyr Ala Ile Pro Ser Lys Gln 75

<210> 449 <211> 89 <212> PRT <213> Homo sapiens

Pro Glu Phe His Ile Glu Ile Leu Ser Ile

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<220>
<221> SIGNAL
<222> -61..-1
<400> 449
Met Asn Ala Ala Ile Asn Thr Gly Pro Ala Pro Ala Val Thr Lys Thr
               -55
                             - -50
Glu Thr Glu Val Gln Asn Pro Asp Val Leu Trp Asp Leu Asp Ile Pro
                 -40
                            -35
Glu Ala Arg Ser His Ala Asp Gln Asp Ser Asn Pro Lys Ala Glu Ala
                                -20
                                       -15
              -25
Leu Leu Pro Cys Asn Leu His Cys Ser Trp Leu His Ser Ser Pro Arg
                 -5
          -10
Pro Asp Pro His Ser His Phe Pro Ser Xaa Arg Arg Cys Pro Leu Pro
 5
       10
                                 15
His Pro Cys Ala Thr Tyr Pro Pro Xaa
                 25
<210> 450
<211> 73
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 450
Met Arg Met Ser Leu Ala Gln Arg Val Leu Leu Thr Trp Leu Phe Thr
   -25
                     -20
                                       -15
Leu Leu Phe Leu Ile Met Leu Val Leu Lys Leu Asp Glu Lys Ala Pro
               - 5
                                  1
Trp Asn Trp Phe Leu Ile Phe Ile Pro Val Trp Ile Phe Asp Thr Ile
         10
                           15
Leu Leu Val Leu Leu Ile Val Lys Met Ala Gly Arg Cys Lys Ser Gly
                      30
Phe Asp Leu Asp Met Asp His Thr Ile
  40
                     4.5
<210> 451
<211> 54
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -34..-1
<400> 451
Met Ile Pro Leu Ile Ser His Leu Ala Glu Ala Ala Pro Pro Thr Ser
                         -25 -20
             -30
Trp Ser Leu Ile Ser Ser Val Leu Asn Val Gly His Leu Leu Phe Ser
          -15
                            -10
                                              -5
Ser Ala Cys Ser Val Ser Leu Glu Ala Leu Ser Thr Arg Asn Ile Lys
                              10
    1
Ala Ile Ile Leu Met Lys
```

20

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<210> 452 <211> 121

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<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -38..-1
<400> 452
Met Glu Ser Pro Gln Leu His Cys Ile Leu Asn Ser Asn Ser Val Ala
         -35
                           -30
Cys Ser Phe Ala Val Gly Ala Gly Phe Leu Ala Phe Leu Ser Cys Leu
 -20 \
                         -15
                                 -10
Ala Phe Leu Val Leu Asp Thr Gln Glu Thr Arg Ile Ala Gly Thr Arg
                         · 5
 -5
                     1
Phe Lys Thr Ala Phe Gln Leu Leu Asp Phe Ile Leu Ala Val Leu Trp
           15
                  20
Ala Val Val Trp Phe Met Gly Phe Cys Phe Leu Ala Asn Gln Trp Gln
         30
                          35
His Ser Pro Pro Lys Glu Xaa Leu Leu Gly Ser Ser Ser Ala Gln Ala
                        50
Ala Ile Gly Xaa His Leu Leu His Pro Cys Leu Asp Ile Pro Xaa
                    65
Leu Pro Gly Xaa Pro Gly Pro Pro Lys
                  80
<210> 453
<211> 166
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 453
Met Ser Thr Val Gly Leu Phe His Phe Pro Thr Pro Leu Thr Arg Ile
                  -30 -25
Cys Pro Ala Pro Trp Gly Leu Arg Leu Trp Glu Lys Leu Thr Leu Leu
                     -15
                                      -10
Ser Pro Gly Ile Ala Val Thr Pro Val Gln Met Ala Gly Lys Lys Asp
-5
                 ı
                     5
Tyr Pro Ala Leu Leu Ser Leu Asp Glu Asn Glu Leu Glu Glu Gln Phe
                            20
          15
Val Lys Gly His Gly Pro Gly Gly Gln Ala Thr Asn Lys Thr Ser Asn
       30
                         35
Cys Val Val Leu Lys Xaa Ile Pro Ser Gly Ile Val Val Lys Cys His
                   50
Gln Thr Arg Ser Val Asp Gln Asn Arg Lys Leu Ala Arg Lys Ile Leu
                 65
                                    70
Gln Glu Lys Val Xaa Val Phe Tyr Asn Gly Glu Asn Ser Pro Val His
                              85
Lys Glu Lys Arg Glu Ala Ala Lys Lys Gln Glu Arg Lys Lys Arg
                            100
Ala Lys Glu Thr Leu Glu Lys Lys Xaa Leu Leu Lys Xaa Leu Trp Glu
       110
                        115
```

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Ser Ser Lys Lys Val His 125

<210> 454 <211> 180 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -26..-1 <400> 454 Met Gly Ile Gln Thr Ser Pro Val Leu Leu Ala Ser Leu Gly Val Gly -25 -20 -15 Leu Val Thr Leu Leu Gly Leu Ala Val Gly Ser Tyr Leu Val Arg Arg - 5 1 Ser Arg Arg Pro Gln Val Thr Leu Leu Asp Pro Asn Glu Lys Tyr Leu 10 15 20 Leu Arg Leu Leu Asp Lys Thr Thr Val Ser His Asn Thr Lys Arg Phe 30 Arg Phe Ala Leu Pro Thr Ala His His Thr Leu Gly Leu Pro Val Gly 45 50 Lys His Ile Tyr Leu Ser Thr Arg Ile Asp Gly Ser Leu Val Ile Arg 60 65 Pro Tyr Thr Pro Val Thr Ser Asp Glu Asp Gln Gly Tyr Val Asp Leu Val Xaa Lys Val Tyr Leu Lys Gly Val His Pro Lys Phe Pro Glu Gly 90 95 Gly Lys Met Ser Xaa Tyr Leu Asp Xaa Leu Lys Val Gly Asp Xaa Val . 110 115 Glu Phe Xaa Gly Pro Ser Gly Leu Leu Thr Tyr Thr Gly Lys Gly His 125 130 Phe Asn Ile Gln Pro Asn Lys Asn Leu His Gln Asn Pro Glu Trp Arg Arg Asn Trp Glu

<210> 455 <211> 91 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -64..-1 <400> 455 Met Thr Pro Arg Ile Leu Ser Glu Val Gln Phe Ser Ala Phe Cys Pro -60 -55 Tyr Trp Thr Ile Ala Arg Ile Leu Glu Arg Val Gly Ser Ala Cys Phe -40 Arg Leu Glu Leu Cys Ala Ala Ile Val Gly Tyr Phe Val Leu Asp Val -30 -25 -20 Arg Thr Phe Leu Phe Ile Val Val Cys Val Ile Cys Val Thr Leu Asn -10 -5 Phe Pro Arg Phe Tyr Phe Leu Cys Leu Ser Ser Leu Thr Ala Phe Gly 10

Thr Pro Pro Ile Gly Val His Ile Pro Ser Pro

20 25

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<210> 456
<211> 257
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 456
Met Arg Arg Ile Ser Leu Thr Ser Ser Pro Val Arg Leu Leu Leu Xaa
          -20
                           -15
                                                  -10
Leu Leu Leu Leu Ile Ala Leu Glu Ile Met Val Gly Gly His Ser
     -5
                          1
Leu Cys Phe Asn Phe Thr Ile Lys Ser Leu Ser Arg Pro Gly Gln Pro
                   15
                                      20
Trp Cys Glu Ala His Val Phe Leu Asn Lys Asn Leu Phe Leu Gln Tyr
                                  35
              30
Asn Ser Asp Asn Asn Met Val Lys Pro Leu Gly Leu Leu Gly Lys Lys
           45
                              50
Val Tyr Ala Thr Ser Thr Trp Gly Glu Leu Thr Gln Thr Leu Gly Glu
                           65
                                              70
Val Gly Arg Asp Leu Arg Met Leu Leu Cys Asp Ile Lys Pro Gln Ile
                       80
Lys Thr Ser Asp Pro Ser Thr Leu Gln Val Xaa Xaa Phe Cys Gln Arg
                                      100
Glu Ala Glu Arg Cys Thr Gly Ala Ser Trp Gln Phe Ala Thr Asn Gly
               110
                                   115
                                                      120
Glu Lys Ser Leu Leu Phe Asp Ala Met Asn Met Thr Trp Thr Val Ile
           125
                                                  135
                              130
Asn His Glu Ala Ser Xaa Ile Lys Glu Thr Trp Lys Lys Asp Arg Xaa
                          145
                                             150
Leu Glu Xaa Tyr Phe Arg Lys Leu Ser Lys Gly Asp Cys Asp His Trp
                      160
                                        165
Leu Arg Glu Phe Leu Gly His Trp Glu Ala Met Pro Xaa Pro Xaa Val
170
                  175
                                     180
Ser Pro Xaa Asn Ala Ser Xaa Ile His Trp Ser Ser Ser Xaa Leu Pro
              190
                                  195
Xaa Xaa Trp Ile Ile Leu Gly Ala Phe Ile Leu Leu Xaa Leu Met Gly
                              210
Ile Val Leu Ile Cys Val Trp Trp Gln Asn Gly Xaa Xaa Ser Thr Xaa
Xaa
```

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<210> 457
<211> 193
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -60..-1
<400> 457
Met Cys Pro Ser Leu Glu Glu Ala Pro Ser Val Lys Gly Thr Leu Pro
```

-60

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Cys Ser Gly Gln Gln Pro Phe Pro Phe Gly Ala Ser Asn Ile Pro -40 -35 Leu Leu Gly Arg Ser Arg Lys Val Ala Arg Gly Ala Pro Val Leu -25 -20 Trp Pro Phe Leu Thr Trp Ile Asn Pro Ala Leu Ser Ile Cys Asp Pro -5 Leu Gly Ser Cys Gly Trp Xaa Cys His Thr Ala Gln Val Pro Ala Pro 10 15[.] Leu Gln Leu Pro Thr Ala Cys Pro Pro Leu Pro His Gly Thr Arg Ala 25 30 Val Gly Pro Thr Pro Gly Leu Leu Pro Glu Ala Ala Pro Xaa Thr 4.5 Xaa Gly Ala Leu Ser Ser Arg Ser Arg His Trp Ser Cys Ser Ile Val 60 65 Xaa Cys Leu His Leu His Xaa Leu Leu Ser Val Glu Thr Arg Xaa Phe 75 Xaa Lys His Leu Leu Val Leu Leu Val Ala Val Ala His Ser Val Leu 90 95 Glu Pro Pro Ala Leu Val Pro Asn Val Gln Cys Glu Met Cys Thr His 105 110 Ser Gly Pro Arg Asp Leu Glu Ala Ala Val Val Ser Pro Ala Pro Trp 120 125

<210> 458 <211> 107 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -28..-1

<400> 458

Met Val Leu Thr Leu Gly Glu Ser Trp Pro Val Leu Val Gly Arg Arg -25

-20 -15 Phe Leu Ser Leu Ser Ala Ala Asp Gly Ser Asp Gly Ser His Asp Ser -5 Trp Asp Val Glu Arg Val Ala Glu Trp Pro Trp Leu Ser Gly Thr Ile 10 Arg Ala Val Ser His Thr Asp Val Thr Lys Lys Asp Leu Lys Val Cys 30 Val Glu Phe Xaa Gly Glu Ser Trp Arg Lys Arg Arg Trp Ile Glu Val 45 Tyr Ser Leu Leu Arg Lys Ala Phe Leu Val Lys His Asn Leu Val Leu 60

Ala Glu Arg Lys Ser Pro Glu Ile Ser Trp Gly

<210> 459 <211> 121 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -13..-1

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<400> 459
Met Leu Val Leu Arg Ser Ala Leu Thr Arg Ala Leu Ala Ser Arg Thr
        -10 -5 1
Leu Ala Pro Gln Met Cys Ser Ser Phe Ala Thr Gly Pro Arg Gln Tyr
                    10
Asp Gly Ile Phe Tyr Glu Phe Arg Ser Tyr Tyr Leu Lys Pro Ser Lys
20
          25
                     . 30
Met Asn Glu Phe Leu Glu Asn Phe Glu Lys Asn Ala Gln Leu Arg Thr
            40
                            45
Ala His Ser Glu Leu Val Gly Tyr Trp Ser Val Xaa Phe Gly Gly Arg
         55
Met Xaa Thr Val Phe His Ile Trp Lys Tyr Asp Asn Phe Ala His Arg
                        75
Thr Glu Phe Gln Lys Ala Leu Ala Lys Asp Lys Glu Trp Gln Glu Gln
                    90
Phe Leu Ile Pro Asn Leu Ala Leu Asn
100 · 105
```

20

<210> 461 <211> 109 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -13..-1 <400> 461 Met Cys Leu Leu Thr Ala Leu Val Thr Gln Val Ile Ser Leu Arg Lys -10 - 5 Asn Ala Glu Arg Thr Cys Leu Cys Lys Arg Arg Trp Pro Trp Xaa Pro 10 15 Ser Pro Arg Ile Tyr Cys Ser Ser Thr Pro Cys Asp Ser Lys Phe Pro 25 3.0 Thr Val Tyr Ser Ser Ala Pro Phe His Ala Pro Leu Pro Val Gln Asn Ser Leu Trp Gly His Pro Leu His Gly Cys Ser Trp Gln Cys His His 55 60 Pro Gln Gly Gln Asn Leu Gln Pro Ala Ser Leu Xaa Thr His Leu Ser 75 Lys Pro Lys Arg His Phe Xaa Lys Lys Xaa Cys Gln Ala

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85 90 95

<210> 462 <211> 143 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -41..-1 <400> 462 Met Ala Thr Ala Thr Glu Gln Trp Val Leu Val Glu Met Val Gln Ala +35 -30 Leu Tyr Glu Ala Pro Ala Tyr His Leu Ile Leu Glu Gly Ile Leu Ile -25 -20 Leu Trp Ile Ile Arg Leu Leu Phe Ser Lys Thr Tyr Lys Leu Gln Glu - 5 Arg Ser Asp Leu Thr Val Lys Glu Lys Glu Glu Leu Ile Glu Glu Trp 15 Gln Pro Glu Pro Leu Val Pro Pro Val Pro Lys Asp His Pro Ala Leu 30 Asn Tyr Asn Ile Val Ser Gly Pro Pro Ser His Lys Thr Val Val Asn 45 Gly Lys Glu Cys Ile Asn Phe Ala Ser Phe Asn Phe Leu Gly Leu Leu 65 Asp Asn Pro Arg Val Lys Ala Ala Ala Leu Ala Ser Leu Lys Lys Tyr 80 Gly Val Gly Thr Cys Gly Pro Cys Gly Phe Tyr Gly Thr Phe Glu 90

<210> 463 <211> 232 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -30..-1

<400> 463 Met Ala Ala Thr Ser Gly Thr Asp Glu Pro Val Ser Gly Glu Leu Val -25 -20 Ser Val Ala His Ala Leu Ser Leu Pro Ala Glu Ser Tyr Gly Asn Xaa -5 Xaa Asp Ile Glu Met Ala Trp Ala Met Arg Ala Met Gln His Ala Glu 10 Val Tyr Tyr Lys Leu Ile Ser Ser Val Asp Pro Gln Phe Leu Lys Leu 25 Thr Lys Val Asp Asp Gln Ile Tyr Ser Glu Phe Arg Lys Asn Phe Glu 40 45 Thr Leu Arg Ile Asp Val Leu Xaa Pro Glu Xaa Leu Lys Ser Glu Ser 60 Ala Lys Glu Pro Pro Gly Tyr Asn Ser Leu Pro Leu Lys Leu Leu Gly Thr Gly Lys Ala Ile Thr Lys Leu Phe Ile Ser Val Phe Arg Thr Lys 90 Lys Glu Arg Lys Glu Ser Thr Met Glu Glu Lys Lys Glu Leu Thr Val

```
105
  100
                                     110
Glu Lys Lys Arg Thr Pro Arg Met Glu Glu Arg Lys Glu Leu Ile Val
115 120 125 130
Glu Lys Lys Lys Arg Lys Glu Ser Thr Glu Lys Thr Lys Leu Thr Lys
            135
                               140
Glu Glu Lys Lys Gly Lys Lys Leu Thr Lys Lys Ser Thr Lys Val Val
                 155
                                          160
Lys Lys Leu Cys Lys Val Tyr Arg Glu Gln His Ser Arg Ser Tyr Asp
            170
                               175
Ser Ile Glu Thr Thr Ser Thr Thr Val Leu Leu Ala Gln Thr Pro Leu
180 185
Val Lys Cys Lys Phe Leu Tyr Asn
                 200
<210> 464
<211> 61
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 464
Met Thr Phe Arg His Gln Asp Asn Ser Leu Met Phe Phe Ser Met Met
-20 -15 -10
Ala Thr Cys Thr Ser Asn Val Gly Phe Thr His Thr Thr Met Asn Cys
                1
Ser Leu Thr Ser Pro Val Asp Phe Lys Asp Leu Leu Arg Val Leu Leu
                     20
Ile Lys Phe Gly Tyr Asp Arg Lys Ser Thr Ile Lys Ser
                        35
<210> 465
<211> 34
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 465
Met Phe Leu Lys Ser Gly Ala Gly Leu Ser Ser Cys Leu Leu Pro Leu
           -15
                             -10
Cys Trp Leu Glu Arg Lys Asp His Gly Arg Arg Pro Ser Xaa His Pro
                       5
                                         10
Gly Arg
  15
<210> 466
<211> 215
<212> PRT
<213> Homo sapiens
<220>
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<221> SIGNAL <222> -54..-1 <400> 466 Met Asn Xaa Tyr Ala Ser Pro Phe Asn Xaa Gln Leu Xaa Tyr Leu Xaa -45 -50 Leu Ser Arg Phe Glu Cys Val His Arg Asp Gly Arg Val Ile Thr Leu -30 -25 Ser Tyr Gln Glu Gln Glu Leu Gln Asp Phe Leu Leu Ser Gln Met Ser -15 Gln His Gln Val His Ala Val Gln Gln Leu Ala Lys Val Met Gly Trp -5 1 Gln Val Leu Ser Phe Ser Asn His Val Gly Leu Gly Pro Ile Glu Ser 15 20 Xaa Gly Asn Ala Ser Ala Ile Thr Val Ala Pro Gln Val Val Thr Met 30 35 Leu Phe Gln Phe Val Met Asp Leu Lys Val Ala Ala Arg Leu Trp Phe 50 Ser Phe Leu Val Thr Asn Val Lys Thr Phe Gln Lys Val Met Phe Tyr 65 70 Lys Ile Thr Asn Gly Val Ile Phe Val Gly His Ser Lys Lys Phe Ser 80 85 Gly Ile Lys Trp Lys Val Xaa Ile Leu Phe Ile Lys Trp Xaa Cys Leu 100 95 Cys Leu His Leu Ala Leu Val Tyr Tyr Asp Phe Phe Gln Met Phe Pro 115 110 Lys Xaa Val Ser Xaa Asn Phe Asp Leu Lys Cys Leu Gln Ile Asn Tyr 125 130 Lys His Lys Glu Glu Ile Thr Ser Lys Arg Val Leu Phe Leu Lys Ile 140 145 150 Ile Ile Arg Lys Cys Phe Ile 160

<210> 468. <211> 85 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -24..-1 <400> 468 WO 99/31236 -335- PCT/IB98/02122 -

Met Cys Ser His Ala Ser Met Ser Phe His Thr Leu Phe His Leu Leu -10 -20 -15 Phe Leu Pro His Tyr Ile Glu Thr Phe Lys Pro Gln Ser Lys His Cys 1 -5 Phe Phe Trp Ile Ala Ala Phe Leu Thr Ser Leu Leu Thr Pro Gln Ser 15 Leu Gln Gly Phe His Ser Ser Leu Cys Ala Leu Arg Ser Gln His Phe 30 35 Pro Ser Thr Cys Asn Cys Phe Cys Tyr Leu Thr Ile Ile Ala Leu Xaa 50 Tyr Trp Asp Asn Leu 60

<210> 469
<211> 51
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 469
Met Leu Arg Ile Ala Leu Thr

Met Leu Arg Ile Ala Leu Thr Leu Ile Pro Ser Met Leu Ser Arg Ala
-15 -10 -5

Ala Gly Trp Cys Trp Tyr Lys Glu Pro Thr Gln Gln Phe Ser Tyr Leu
1 5 10 15

Cys Leu Pro Cys Leu Ser Trp Asn Lys Lys Gly Asn Val Leu Gln Leu
20 25 30

Pro Asn Phe
35

<210> 470 <211> 67 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -43..-1

<210> 471 <211> 63 <212> PRT <213> Homo sapiens

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<220>
<221> SIGNAL
<222> -15..-1
<400> 471
Met Gly Ile Leu Ser Thr Val Thr Ala Leu Thr Phe Ala Arg Ala Leu
                   -10
Asp Gly Cys Arg Asn Gly Ile Ala His Pro Ala Ser Glu Lys His Arg
                               10
                                                15
Leu Glu Lys Cys Arg Glu Leu Glu Ser Ser His Ser Ala Pro Gly Ser
      20
                           25
                                      30
Thr Gln His Arg Arg Lys Thr Thr Arg Arg Asn Tyr Ser Ser Ala
                       40
                                          45
<210> 472
<211> 179
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -58..-1
<400> 472
Met Ser Thr Gly Gln Leu Tyr Arg Met Glu Asp Ile Gly Arg Phe His
          ~55
                               -50
Ser Gln Gln Pro Gly Ser Leu Thr Pro Ser Ser Pro Thr Val Gly Glu
                           -35
                                               -30
Ile Ile Tyr Asn Asn Thr Arg Asn Thr Leu Gly Trp Ile Gly Gly Ile
                       -20
                                           -15
Leu Met Gly Ser Phe Gln Gly Thr Ile Ala Gly Gln Gly Thr Gly Ala
                   - 5
Thr Ser Ile Ser Glu Leu Cys Lys Gly Gln Glu Leu Glu Pro Ser Gly
          10
                              15
Ala Gly Leu Thr Val Ala Pro Pro Gln Ala Val Ser Leu Gln Gly Ile
                          30
       25
Tyr Thr Leu Pro Trp Leu Leu Gln Leu Phe His Ser Thr Ala Leu Xaa
                      45
                                           50
Xaa Xaa Gln Gln Pro Asn Gly Ser Leu Ser Leu Asn Ile Ser Ser Ser
                   60
His Ala Pro Xaa Pro Xaa Thr Cys Thr Leu Glu Pro Gly Val Asp Pro
               75
                                   80
                                                       85
Thr Arg Xaa Val Cys Ile Asn Pro His Pro Pro Pro Pro Ile Leu Lys
                               95
Xaa Pro Leu Ser Pro Tyr Pro Lys Pro Gln Leu Gly Thr His Ala Gly
                          110
                                               115
Gln Val Asn
   120
<210> 473
<211> 238
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
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<222> -71..-1

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<400> 473 Met Xaa Xaa Phe Thr Asp Pro Ser Ser Val Asn Glu Lys Lys Arg Arg -65 -60 Glu Arg Glu Glu Arg Gln Asn Ile Val Leu Trp Arg Gln Pro Leu Ile -50 -45 Thr Leu Gln Tyr Phe Ser Leu Glu Ile Leu Val Ile Leu Lys Glu Trp -35 -30 -25 Thr Ser Lys Leu Trp His Arg Gln Ser Ile Val Val Ser Phe Leu Leu -20 -15 Leu Leu Ala Gly Leu Ile Ala Thr Tyr Tyr Val Glu Gly Val His Gln Gln Tyr Val Gln Arg Ile Glu Lys Gln Phe Leu Leu Tyr Ala Tyr Trp Ile Gly Leu Gly Ile Leu Ser Ser Val Gly Leu Gly Thr Gly Leu His 30 35 Thr Phe Leu Leu Tyr Leu Gly Pro His Ile Ala Ser Val Thr Leu Ala 45 50 Ala Tyr Glu Cys Asn Ser Val Asn Phe Pro Glu Pro Pro Tyr Pro Asp 70 65 Gln Ile Ile Cys Pro Asp Glu Glu Gly Thr Glu Gly Thr Ile Ser Leu Trp Ser Ile Ile Ser Lys Val Arg Ile Glu Ala Cys Met Trp Gly Ile 100 Gly Thr Ala Ile Gly Glu Leu Pro Pro Tyr Phe Met Ala Arg Ala Ala 110 115 Arg Leu Ser Gly Ala Glu Pro Asp Asp Glu Glu Tyr Gln Glu Phe Glu 125 130 Glu Met Leu Glu His Ala Glu Ser Ala Gln Val Arg Thr Val Gly Ile 145 Glu Asn Arg Thr Leu Tyr Phe Phe Leu Lys Arg Leu Leu Arg

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<210> 474
<211> 178
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 474
Met Glu Arg Gln Ser Arg Val Met Ser Glu Lys Asp Glu Tyr Gln Phe
                           -30
                                               -25
Gln His Gln Gly Ala Val Glu Leu Leu Val Phe Asn Phe Leu Leu Ile
                       -15
                                          -10
Leu Thr Ile Leu Thr Ile Trp Leu Phe Lys Asn His Arg Phe Arg Phe
                                  5
Leu His Glu Thr Gly Gly Ala Met Val Tyr Gly Leu Xaa Met Gly Leu
                               20
Ile Leu Xaa Tyr Ala Thr Ala Pro Thr Asp Ile Glu Ser Gly Xaa Val
                            35
Tyr Asp Cys Val Lys Leu Thr Phe Ser Pro Ser Thr Leu Leu Val Asn
Ile Thr Asp Gln Val Tyr Glu Tyr Lys Tyr Lys Arg Glu Ile Ser Gln
                   65
His Xaa Ile Asn Pro His Xaa Gly Asn Ala Ile Leu Glu Lys Met Thr
                                   85
Phe Asp Pro Xaa Ile Phe Phe Asn Val Leu Leu Pro Pro Ile Ile Phe
```

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```
100
                                             105
His Ala Gly Tyr Ser Leu Lys Lys Arg His Phe Phe Gln Asn Leu Gly .
 110 115
                               120
Ser Ile Leu Thr Tyr Ala Phe Leu Gly Thr Ala Ile Ser Cys Ile Val
125
              130
                                   135
Ile Gly
140
<210> 475
<211> 96
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 475
Met Ser Met Gln Phe Leu Phe Lys Met Val Ala Leu Cys Cys Cys Leu
              -15
                                      -10
Trp Lys Ile Ser Gly Cys Glu Glu Val Pro Leu Thr Tyr Asn Leu Leu
                 1
Lys Cys Leu Leu Asp Lys Ala His Cys Val Leu Leu Thr Pro Cys Gly
                        20
Tyr Ile Phe Ser Leu Ile Ser Pro Glu Ile Leu Lys Leu Thr Leu Ile
Thr Leu Xaa Ile Leu Leu Ile Leu Lys Asn Leu His Leu Leu Trp Leu
              50
                               55
Thr Val Ser Ser Xaa Cys Val His Arg Ser Ser Ala Arg Lys Glu Lys
               65 70
<210> 476
<211> 41
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -24..-1
<400> 476
Met His Thr Phe Ala Asn Asp Arg Gly Leu Tyr Arg Ile Leu Leu Leu
          -20 -15
His Phe Tyr Cys Leu Leu Arg Ser Ser Glu Tyr Ile Leu Gly Tyr Lys
                 1
         -5
Val Leu Gly Val Phe Phe Pro Ile Leu
   10
<210> 477
<211> 113
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
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<222> -27..-1

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<400> 477 Met Arg Xaa Lys Trp Lys Met Gly Gly Met Lys Tyr Ile Phe Ser Leu -20 Leu Phe Phe Leu Leu Glu Gly Gly Xaa Thr Glu Gln Val Xaa His ~5 Ser Glu Thr Tyr Cys Met Phe Gln Asp Lys Lys Tyr Arg Val Gly Glu 10 15 Arg Trp His Pro Tyr Leu Glu Pro Tyr Gly Leu Val Tyr Cys Val Asn 25 . 30 Cys Ile Cys Ser Glu Asn Gly Asn Val Leu Cys Ser Arg Val Arg Cys 45 Pro Asn Val His Cys Leu Ser Pro Val His Ile Pro His Leu Cys Cys 60 Pro Arg Cys Pro Glu Asp Ser Leu Pro Pro Val Asn Asn Xaa Val Thr 75 80 Ser

<210> 478 <211> 250 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -18..-1

<400> 478 Met Arg Ile Leu Gln Leu Ile Leu Leu Ala Leu Ala Thr Gly Leu Val -15 -10 Gly Glu Thr Arg Ile Ile Lys Gly Phe Glu Cys Lys Pro His Ser Gln Pro Trp Gln Ala Ala Leu Phe Glu Lys Thr Arg Leu Leu Cys Gly 20 25 Ala Thr Leu Ile Ala Pro Arg Trp Leu Leu Thr Ala Ala His Cys Leu 35 40 Lys Pro Arg Tyr Ile Xaa His Leu Gly Gln His Asn Leu Gln Lys Glu Glu Gly Cys Glu Gln Thr Arg Thr Ala Thr Glu Ser Phe Pro His Pro 70 Gly Phe Asn Asn Ser Leu Pro Asn Lys Asp Xaa Xaa Asn Asp Ile Met 80 85 90 Leu Val Xaa Met Xaa Ser Pro Val Ser Ile Thr Trp Ala Val Arg Pro 100 105 Leu Thr Leu Ser Ser Arg Cys Val Thr Ala Gly Thr Ser Cys Leu Ile 115 120 Ser Gly Trp Gly Ser Thr Ser Ser Pro Gln Leu Arg Leu Pro His Thr 130 135 140 Leu Arg Cys Ala Asn Ile Thr Ile Ile Glu His Gln Lys Cys Glu Asn 145 150 155 Ala Tyr Pro Gly Asn Ile Thr Asp Thr Met Val Cys Ala Ser Val Gln 165 170 Glu Gly Gly Lys Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val 180 185 Cys Asn Gln Ser Leu Gln Gly Ile Ile Ser Trp Gly Gln Asp Pro Cys 195 200 Ala Ile Thr Arg Lys Pro Gly Val Tyr Thr Lys Val Cys Lys Tyr Val 210 215

230

Asp Trp Ile Gln Glu Thr Met Lys Asn Asn

225

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<210> 479

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<211> 151
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 479
Met Ala Ala Ser Thr Ser Met Val Pro Val Ala Val Thr Ala Ala Val
                      -15
                            -10
Ala Pro Val Leu Ser Ile Asn Ser Asp Phe Ser Asp Leu Arg Glu Ile
Lys Lys Gln Leu Leu Ile Ala Gly Leu Thr Arg Glu Arg Gly Leu
                              20
Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser Leu Pro Ala
                          35
                                             40
Leu Pro Leu Ala Glu Leu Gln Pro Pro Pro Pro Ile Thr Glu Glu Asp
                       50
                                          55
Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr Phe Asp Val
                                      70
                   65
Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys Asn Ala Arg
Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val Arg Ala Ile
           95
                               100
                                                 105
Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe Arg Thr Asn
      110
                          115
Gly Lys Val Lys Ser Phe Lys
  125
<210> 480
<211> 239
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -25..-1
<400> 480
Met Pro Arg Lys Arg Lys Cys Asp Leu Arg Ala Val Arg Val Gly Leu
                   -20
                                      -15
Leu Leu Gly Gly Gly Val Tyr Gly Ser Arg Phe Arg Phe Thr Phe
               -5
                                  1
Pro Gly Cys Arg Ala Leu Ser Pro Trp Arg Val Arg Xaa Gln Arg Arg
      10
                          15
                                              20
Arg Cys Glu Met Ser Thr Met Phe Ala Asp Thr Leu Leu Ile Val Phe
                       30
Ile Ser Val Cys Thr Ala Leu Leu Ala Glu Gly Ile Thr Trp Val Leu
                 45
                                      50
Val Tyr Arg Thr Asp Lys Tyr Lys Arg Leu Lys Ala Glu Val Glu Lys
               60
                                   65
Gln Ser Lys Lys Leu Glu Lys Lys Lys Glu Thr Ile Thr Glu Ser Ala
                              80
Gly Arg Gln Gln Lys Lys Ile Glu Arg Xaa Xaa Xaa Xaa Leu Xaa
```

Asn Asn Asn Arg Asp Leu Ser Met Val Arg Met Lys Ser Met Phe Ala 110 Ile Gly Phe Cys Phe Thr Ala Leu Met Gly Met Phe Asn Ser Ile Phe 125 130 Asp Gly Arg Val Val Ala Lys Leu Pro Phe Thr Pro Leu Ser Xaa Xaa 140 145 Xaa Gly Leu Ser His Arg Asn Leu Leu Gly Asp Asp Thr Thr Asp Cys 155 160 Ser Phe Ile Phe Leu Xaa Ile Leu Cys Thr Met Ser Ile Arg Gln Asn 175 Ile Gln Lys Ile Leu Gly Leu Ala Pro Ser Arg Ala Ala Thr Lys Gln 190 195 Ala Gly Gly Phe Leu Gly Pro Pro Pro Ser Gly Lys Phe Ser 210 205

<210> 481 <211> 208 <212> PRT <213> Homo sapiens

<221> SIGNAL <222> -92..-1

<400> 481 Met Arg Glu Pro Gln Lys Arg Thr Ala Thr Ile Ala Lys Xaa Xaa Ala -85 Xaa Glu Gly Leu Arg Asp Pro Tyr Gly Arg Leu Cys Gly Ser Glu His -70 -65 Pro Arg Arg Pro Pro Glu Arg Pro Glu Glu Asp Pro Ser Thr Pro Glu -55 -50 Glu Ala Ser Thr Thr Pro Glu Glu Ala Ser Ser Thr Ala Gln Ala Gln -40 -35 Lys Pro Ser Val Pro Arg Ser Asn Phe Gln Gly Thr Lys Lys Ser Leu -25 -20 Leu Met Ser Ile Leu Ala Leu Ile Phe Ile Met Gly Asn Ser Ala Lys -5 Glu Ala Leu Val Trp Lys Val Leu Gly Lys Leu Gly Met Gln Pro Gly 15 10 Arg Xaa His Ser Ile Phe Gly Asp Pro Lys Lys Ile Val Thr Glu Xaa 25 30 Phe Val Arg Arg Gly Tyr Leu Ile Tyr Xaa Pro Val Pro Arg Xaa Ser 45 Pro Val Glu Tyr Xaa Phe Phe Trp Gly Pro Arg Ala His Val Glu Ser 60 Ser Xaa Leu Lys Xaa Xaa His Phe Val Ala Arg Val Arg Asn Arg Cys 75 80 Ser Lys Asp Trp Pro Cys Asn Tyr Asp Trp Asp Ser Asp Asp Asp Ala . 90 95 Glu Val Glu Ala Ile Leu Asn Ser Gly Ala Xaa Gly Tyr Ser Ala Pro

110

<210> 482 <211> 86 <212> PRT <213> Homo sapiens

105

<220>

<221> SIGNAL <222> -39..-1 <400> 482 Met Asn Val Gly Thr Ala His Xaa Xaa Val Asn Pro Asn Thr Arg Val -30 Met Asn Ser Arg Gly Ile Trp Leu Ser Tyr Val Leu Ala Ile Gly Leu -20 -15 - 1.0 Leu His Ile Val Leu Leu Ser Ile Pro Phe Val Ser Val Pro Val Val -5 1 Trp Thr Leu Thr Asn Leu Ile His Asn Met Gly Met Tyr Ile Phe Leu 10 15 20 His Thr Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys Ala 30 Arg Leu Leu Thr His Trp 45

<210> 483
<211> 40
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -27..-1

<210> 484 <211> 65 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -16..-1 <400> 484

Met Leu Gly Phe Phe Leu Phe Leu Ser Phe Val Leu Met Tyr Asp Gly
-15 -10 -5

Leu Arg Leu Phe Gly Ile Leu Ser Thr Cys Arg Val His His Thr Met
1 5 10 15

Asn Gln Phe Leu Ile Asp Ile Ser Ser Phe Thr Ser Arg Val Lys Lys
20 25 30

Lys Ile Phe Leu Phe Tyr Ala Phe Xaa Gly Cys Xaa Phe Gln Ser Ala
35 40 45

<210> 485 <211> 130 WO 99/31236 -343 - PCT/IB98/02122 -

<212> PRT

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<213> Homo sapiens
<220>
<221> SIGNAL
<222> -55..-1
<400> 485
Met Ala Met Trp Asn Arg Pro Xaa Xaa Xaa Leu Pro Gln Gln Pro Leu
                -50
                                    -45
Xaa Ala Glu Pro Thr Ala Glu Gly Glu Pro His Leu Pro Thr Gly Arg
                                   -30
                                                      -25
               -35
Xaa Xaa Thr Glu Ala Asn Arg Phe Ala Tyr Ala Ala Leu Cys Gly Ile
           -20
                              -15
                                       -10
Ser Leu Ser Gln Leu Phe Pro Glu Pro Glu His Ser Ser Phe Cys Thr
                          1
Glu Phe Met Ala Gly Leu Val Xaa Trp Leu Glu Leu Ser Glu Ala Val
                  15
                                     20
Leu Pro Thr Met Thr Ala Phe Ala Ser Gly Leu Gly Gly Glu Gly Xaa
            30
                                   35
Xaa Cys Val Cys Ser Asn Phe Thr Glu Gly Pro His Leu Glu Gly Arg
           45
                               50
Pro Asp Gly Asp His Ser Gly Pro Ser Glu Leu Leu Thr Gln Gly Trp
                          65
Ala Leu
  75
<210> 486
<211> 209
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -84..-1
<400> 486
Met Val Asn Phe Pro Gln Lys Ile Ala Gly Glu Leu Tyr Gly Pro Leu
               -80
                                   -75
                                                      -70
Met Leu Val Phe Thr Leu Val Ala Ile Leu Leu His Gly Met Lys Thr
           -65
                               -60
Ser Asp Thr Ile Ile Arg Glu Gly Thr Leu Met Gly Thr Ala Ile Gly
       -50
                           -45
                                               -40
Thr Cys Phe Gly Tyr Trp Leu Gly Val Ser Ser Phe Ile Tyr Phe Leu
                       -30
                                          -25
Ala Tyr Leu Cys Asn Ala Gln Ile Thr Met Leu Gln Met Leu Ala Leu
                   -15
                                      -10
Leu Gly Tyr Gly Leu Phe Gly His Cys Ile Val Leu Phe Ile Thr Tyr
                               5
Asn Ile His Leu Arg Ala Leu Phe Tyr Leu Phe Trp Leu Leu Val Gly
                           20
Gly Leu Ser Thr Leu Arg Met Val Ala Val Leu Val Ser Arg Thr Val
                       35
                                           40
Gly Pro Thr Xaa Arg Xaa Leu Leu Cys Gly Thr Leu Ala Ala Leu His
                   50
Met Leu Phe Leu Leu Tyr Leu His Phe Ala Tyr His Lys Xaa Val Xaa
                                   70
Gly Ile Leu Asp Thr Leu Glu Gly Pro Asn Ile Pro Pro Ile Gln Arg
                               85
```

Val Pro Arg Asp Ile Pro Ala Met Leu Pro Ala Ala Arg Leu Pro Thr

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```
100
Thr Val Leu Asn Ala Thr Ala Lys Ala Val Ala Val Thr Leu Gln Ser
           115
                                          120
His
125
<210> 487
<211> 36
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -17..-1
<400> 487
Met Gly Trp Gln Arg Trp Trp Cys Phe His Leu Gln Ala Glu Ala Ser
                        -10
                                            -5
Ala His Pro Pro Gln Gly Leu Gln Ala Gln Phe Ser Cys Cys Pro Trp
                  5
Val Gly Ile Cys
<210> 488
<211> 44
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -29..-1
<400> 488
Met Met Ser Ser Glu Leu Arg Arg Asn Pro His Phe Leu Lys Ser Asn
            -25
                         -20
Leu Phe Leu Gln Leu Leu Val Ser His Glu Ile Val Cys Ala Thr Glu
           -10
                              -5
Thr Val Thr Thr Asn Phe Leu Arg His Glu Lys Ala
                      10
<210> 489
<211> 163
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -52..-1
<400> 489
Met Glu His Tyr Arg Lys Ala Gly Ser Val Glu Leu Pro Ala Pro Ser
                           -45
                                              -40
Pro Met Pro Gln Leu Pro Pro Asp Thr Leu Glu Met Arg Val Arg Asp
                      -30
                                          -25
Gly Ser Lys Ile Arg Asn Leu Leu Gly Leu Ala Leu Gly Arg Leu Glu
                   -15
                                      -10
Gly Gly Ser Ala Arg His Val Val Phe Ser Gly Ser Gly Arg Ala Ala
```

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```
. 5
                                              10
              1
Gly Lys Ala Val Ser Cys Ala Glu Ile Val Lys Arg Arg Val Pro Gly
             20
                                  25
Leu His Gln Leu Thr Lys Leu Xaa Phe Leu Gln Thr Glu Asp Ser Trp
                     35
Val Pro Xaa Ser Pro Asp Thr Gly Leu Xaa Pro Leu Thr Val Arg Arg
               50
                                 55
His Val Pro Ala Xaa Trp Val Leu Leu Xaa Arg Asp Pro Leu Asp Pro
                              70
            65
Asn Glu Cys Gly Tyr Gln Pro Pro Gly Ala Pro Pro Gly Leu Gly Ser
                         85
Met Pro Ser Ser Ser Cys Gly Pro Arg Ser Xaa Lys Arg Ala Xaa Xaa
Thr Arg Ser
   110
<210> 490
<211> 64
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -47..-1
<400> 490
Met His Gly Phe Glu Ile Ile Ser Leu Lys Glu Glu Ser Pro Leu Gly
               -40
Lys Val Ser Gln Gly Pro Leu Phe Asn Val Thr Ser Gly Ser Ser Ser
                     -25
Pro Val Thr Trp Leu Gly Leu Leu Ser Phe Gln Asn Leu His Cys Phe
-15 -10
                         -5
Pro Asp Leu Pro Thr Glu Met Pro Leu Xaa Ala Lys Gly Xaa Asn Thr
                           10
<210> 491
<211> 218
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -50..-1
<400> 491
Met His His Gly Leu Thr Pro Leu Leu Gly Val His Glu Gln Lys
               -45
                                   -40
Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala
             -30
                                -25
                                            -20
Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly
          -15
                          -10
Ser Ala Ser Ile Val Ser Leu Leu Glu Gln Asn Ile Asp Val Ser
                                       10
Ser Gln Asp Leu Ser Gly Gln Thr Ala Lys Lys Tyr Ala Val Ser Ser
                 20
                                    25
Arg His Asn Val Ile Cys Gln Leu Leu Ser Asp Tyr Lys Xaa Lys Gln
```

40

Xaa Leu Lys Val Ser Ser Glu Asn Ser Asn Pro Xaa Gln Asp Leu Lys

35

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```
55
Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Lys Gly Ser Glu Asn Ser
                                 75
                        70
Gln Pro Glu Glu Met Ser Gln Glu Pro Glu Ile Asn Xaa Gly Gly Asp
                   85
Arg Lys Val Glu Xaa Xaa Met Lys Lys His Gly Ser Xaa His Met Gly
           100
                                   105
Phe Pro Xaa Asn Leu Xaa Asn Gly Ala Thr Ala Asp Asn Gly Asp Asp
              115
                                120
Gly Leu Ile Pro Pro Xaa Lys Xaa Xaa Thr Pro Glu Ser Xaa Gln Phe
                             135
Pro Asp Thr Glu Asn Glu Gln Tyr His Arg Asp Phe Ser Gly His Pro
       145
                        150
Xaa Phe Pro Thr Thr Leu Pro Ile Lys Gln
                     165
```

<210> 492 <211> 216 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1

<400> 492 Met Val Cys Val Leu Val Leu Ala Ala Ala Gly Ala Val Ala Val -15 -10 -5 Phe Leu Ile Leu Arg Ile Trp Val Val Leu Arg Ser Met Asp Val Thr 10 Pro Arg Glu Ser Leu Ser Ile Leu Val Val Ala Gly Ser Gly Gly His 25 Thr Thr Glu Ile Leu Arg Leu Leu Gly Ser Leu Ser Asn Ala Tyr Ser 40 45 Pro Arg His Tyr Val Ile Ala Asp Thr Asp Glu Met Ser Ala Asn Lys Ile Asn Ser Phe Glu Leu Xaa Arg Xaa Asp Arg Xaa Pro Ser Asn Met 75 70 Xaa Thr Lys Tyr Tyr Ile His Arg Ile Pro Xaa Ser Arg Glu Val Gln 85 90 Gln Ser Trp Pro Ser Thr Val Xaa Thr Thr Leu His Ser Met Trp Leu 105 110 Ser Xaa Pro Leu Ile His Arg Val Lys Pro Xaa Leu Val Leu Cys Asn 120 125 Gly Pro Gly Thr Cys Val Pro Ile Cys Val Ser Ala Leu Leu Leu Gly 135 140 Ile Leu Gly Ile Lys Lys Val Ile Ile Val Tyr Val Glu Ser Ile Cys 150 155 Arg Val Lys Thr Leu Ser Met Ser Gly Lys Ile Leu Phe His Leu Ser 170 Asn Tyr Phe Ile Val Gln Trp Pro Ala Leu Lys Glu Lys Tyr Pro Lys 185 190 Ser Val Tyr Leu Gly Arg Ile Val

<210> 493
<211> 134
<212> PRT

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<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 493
Met Pro Leu Gly Ala Arg Ile Leu Phe His Gly Val Phe Tyr Ala Gly
             -15 -10 -5
Gly Phe Ala Ile Val Tyr Tyr Leu Ile Gln Lys Phe His Ser Arg Thr
Leu Tyr Tyr Lys Leu Ala Val Glu Gln Leu Gln Xaa His Pro Glu Ala
           20
 15
Gln Glu Ala Leu Gly Pro Pro Leu Asn Ile His Tyr Leu Lys Leu Ile
30
                 35
                    40
Asp Arg Glu Asn Phe Val Asp Ile Val Xaa Ala Lys Leu Lys Ile Pro
       . 50 55 60
Val Ser Gly Ser Lys Ser Glu Gly Leu Leu Tyr Val His Ser Ser Arg
                           70
Gly Gly Pro Phe Gln Arg Trp His Leu Asp Glu Val Phe Leu Glu Leu
                      85
Lys Asp Gly Gln Gln Ile Pro Val Phe Lys Leu Ser Gly Glu Asn Gly
Asp Glu Val Lys Lys Glu
<210> 494
<211> 85
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 494
Met Ala Val Thr Ala Leu Ala Ala Xaa Thr Trp Leu Gly Val Trp Gly
 -15 -10 -5
Val Arg Thr Met Gln Ala Arg Gly Phe Gly Ser Asp Gln Ser Glu Asn
                            10
Val Asp Arg Gly Ala Gly Ser Ile Arg Glu Ala Gly Gly Ala Phe Gly
               . 25
Lys Arg Glu Gln Ala Glu Glu Glu Arg Tyr Phe Arg Ala Gln Ser Thr
                 40
                                         45
Glu Gln Leu Ala Xaa Leu Lys Lys Xaa His Glu Glu Glu Ile Val His
                 55
His Arg Glu Gly Asp
65
<210> 495
<211> 292
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
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<222> -29..-1

```
<400> 495
Met His Gly Leu Leu His Tyr Leu Phe His Thr Arg Asn His Thr Phe
                               -20
            -25
Ile Val Leu His Leu Val Leu Gln Gly Met Val Tyr Thr Glu Tyr Thr
                               - 5
           -10
Trp Glu Val Phe Gly Tyr Cys Gln Glu Leu Glu Leu Ser Leu His Tyr
                       10
Leu Leu Leu Pro Tyr Leu Leu Cly Val Asn Leu Phe Phe Thr
                   25
                                      30
Leu Thr Cys Gly Thr Asn Pro Gly Ile Ile Thr Lys Ala Asn Glu Leu
               40
                                  45
Leu Phe Leu His Val Tyr Glu Phe Asp Glu Xaa Met Phe Pro Lys Asn
                              60
Val Arg Cys Ser Thr Cys Asp Leu Arg Lys Pro Ala Arg Ser Xaa His
                          75
                                             80
Cys Xaa Val Cys Asn Trp Cys Val His Arg Phe Xaa His His Cys Val
                     90
                                         95
Trp Val Asn Asn Cys Ile Gly Ala Trp Asn Ile Arg Xaa Phe Leu Ile
                                   110
                  105
Tyr Val Leu Thr Leu Thr Ala Ser Ala Ala Thr Val Ala Ile Val Ser
              120
                                  125
Thr Thr Phe Leu Val His Leu Val Val Met Ser Asp Leu Tyr Gln Glu
           135
                              140
Thr Tyr Ile Asp Asp Leu Gly His Leu His Val Met Asp Thr Val Phe
                          155
                                              160
Leu Ile Gln Tyr Leu Phe Leu Thr Phe Pro Arg Ile Val Phe Met Leu
                                          175
                      170
Gly Phe Val Val Leu Xaa Phe Leu Leu Gly Gly Tyr Leu Leu Phe
                                     190 .
                  185
Val Leu Tyr Leu Ala Ala Thr Asn Gln Thr Thr Asn Glu Trp Tyr Arg
              200
                                 205
Xaa Asp Trp Ala Trp Cys Gln Arg Cys Pro Leu Val Ala Trp Pro Pro
                             220
                                                 225
Ser Ala Glu Pro Gln Val His Arg Asn Ile His Ser His Gly Leu Arg
                                   240
                         235
Xaa Asn Leu Gln Glu Ile Phe Leu Pro Ala Phe Pro Cys His Glu Arg
                     250
Lys Lys Gln Glu
260
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<210> 496
<211> 122
<212> PRT
<213> Homo sapiens
<220>
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<221> SIGNAL <222> -56..-1

 Phe Cys Ala
 Ser Phe Phe Pro Ser Gly Xaa Leu Ser Pro Pro Gly Pro Leu 30
 35
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 Pro Gly Val Arg Gly Leu Pro Leu Pro Ser Val Phe Tyr Ser Cys Gly 45
 50
 55

 Ala His Pro Lys Val Leu Lys Val Ala Leu 60
 65
 65

<210> 497 <211> 59 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -28..-1 <400> 497 Met Leu Xaa Leu Ser Arg Ala Thr Lys Xaa Gly Arg Ala Arg Trp Leu -25 -20 Met Pro Val Ile Pro Ala Leu Gln Glu Ala Xaa Ala Gly Gly Ser Arg -10 -5 Gly Gln Glu Phe Glu Thr Ser Leu Ala Asn Met Glu Thr Glu Ala Gly 10 Glu Leu Leu Lys Pro Arg Arg Arg Leu Gln

<210> 498
<211> 99
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -13..-1
<400> 498

Met His Leu Leu Ser Asn Trp Ala Asn Pro Ala Ser Ser Arg Arg Pro -10 -5 Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Leu Ala His 10 15 Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys Trp Arg Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn Ser Ser 40 45 Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr Pro Met 55 60 Arg Arg Ser Ser Cys His Leu Glu Cys Xaa Val Ile Phe Leu Leu Gly 70 Arg Gln Leu 85

<210> 499 <211> 99 <212> PRT <213> Homo sapiens WO 99/31236 -350- PCT/IB98/02122 -

<220> <221> SIGNAL <222> -13..-1 <400> 499 Met His Leu Leu Ser Asn Trp Ala Asn Pro Ala Ser Ser Arg Arg Pro -10 - 5 Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Leu Ala His 15 10 Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys Trp Arg 25 20 Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn Ser Ser 45 40 Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr Pro Met 60 Arg Arg Ser Ser Cys His Leu Xaa Cys Gln Val Ile Phe Leu Leu Gly 75 70 Arg Gln Leu 85 <210> 500 <211> 108 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -25..-1 <400> 500 Met Ser Leu Thr Ser Ser Ser Ser Val Arg Val Glu Trp Ile Ala Ala -15 -10 -20 Val Thr Ile Ala Ala Gly Thr Ala Ala Ile Gly Tyr Leu Ala Tyr Lys 1 -5 Arg Phe Tyr Val Lys Asp His Arg Asn Lys Ala Met Ile Asn Leu His . 10 15 Ile Gln Lys Asp Asn Pro Lys Ile Val His Ala Phe Asp Met Glu Asp 30 Leu Gly Asp Lys Ala Val Tyr Cys Arg Cys Trp Arg Ser Lys Lys Phe 50 45 Pro Phe Cys Asp Gly Ala His Thr Lys His Asn Glu Glu Thr Gly Asp 70 60 65 Asn Val Gly Pro Leu Ile Ile Lys Lys Lys Glu Thr 80 75 <210> 501

10 Gln Gly Arg Arg Leu Gly Ala Glu Ser Arg Thr Leu Leu Val Ile Ala . 30 25 His Pro Asp Asp Glu Ala Met Phe Phe Ala Pro Thr Val Leu Gly Leu 40 45 Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys Phe Ser Ala Gly Asn . 60 55 Tyr Tyr Asn Gln Gly Glu Thr Arg Lys Lys Glu Leu Leu Gln Ser Cys 75 70 Asp Val Leu Gly Ile Pro Leu Ser Ser Val Met Ile Ile Asp Asn Arg 90 Asp Phe Pro Xaa Asp Pro Gly Met Gln Trp Asp Thr Xaa His Val Ala 105 Xaa Val Leu Leu Gln His Ile Glu Val Asn Gly Ile Asn Leu Val Val 120 125 Thr Phe Asp Ala Gly Gly Xaa Ser Gly His Ser Asn His Ile Ala Leu 135 140 145 Tyr Ala Ala Val Arg Lys Leu Glu Gly Gln Ile Cys Lys Pro Cys Gly 150 155 Thr Gly Gln Asp Phe Lys Glu 165

<210> 502 <211> 98 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1 <400> 502

Met Glu Ala Met Trp Leu Leu Cys Val Ala Leu Ala Val Leu Ala Trp -15 -10 -5 1 Gly Phe Leu Trp Val Trp Asp Ser Ser Glu Arg Met Lys Ser Arg Glu 10 Gln Gly Xaa Arg Leu Gly Ala Glu Ser Arg Thr Leu Leu Val Ile Ala 25 His Pro Asp Asp Glu Ala Met Phe Phe Ala Pro Thr Val Leu Gly Leu Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys Phe Ser Ala Val Phe 55 60 Arg Arg Glu Leu Ser Glu Tyr Thr Glu Xaa Leu Thr Ser Glu Pro Leu

Xaa Ala

<210> 503 <211> 183 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -57..-1

Met Asp Val Thr Gly Asp Glu Glu Glu Glu Ile Lys Gln Glu Ile Asn -55 -50

Met Leu Lys Lys Tyr Ser His His Arg Asn Ile Ala Thr Tyr Tyr Gly -35 Ala Phe Ile Lys Lys Asn Pro Pro Gly Met Asp Asp Gln Leu Trp Leu -25 -20 -15 Val Met Glu Phe Cys Gly Ala Gly Ser Val Thr Asp Leu Ile Lys Asn Thr Lys Gly Asn Thr Leu Lys Glu Glu Trp Ile Ala Tyr Ile Cys Xaa 10 15 20 Glu Ile Leu Arg Gly Leu Xaa His Leu His Gln His Lys Val Ile His 30 35 Arg Xaa Ile Lys Gly Gln Asn Val Leu Leu Thr Glu Asn Ala Glu Val 50 45 Lys Leu Val Asp Phe Gly Xaa Xaa Ala Gln Leu Asp Arg Thr Val Gly Arg Xaa Asn Thr Phe Ile Gly Thr Pro Tyr Trp Met Ala Pro Xaa Val 80 Ile Ala Cys Asp Glu Asn Pro Xaa Ala Thr Tyr Asp Phe Lys Xaa Asp 100 95 90 Leu Trp Ser Leu Gly Ile Thr Ala Ile Glu Met Ala Glu Gly Leu Pro 110 Leu Ser Val Thr Cys Thr Pro

<210> 504 <211> 140 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -14..-1

<400> 504

Met Phe Leu Thr Ala Leu Leu Trp Arg Gly Arg Ile Pro Gly Arg Gln -10 - 5 Trp Ile Gly Lys His Arg Arg Pro Arg Phe Val Ser Leu Arg Ala Lys 10 Gln Asn Met Ile Arg Arg Leu Glu Ile Glu Ala Glu Asn His Tyr Trp 25 Leu Ser Met Pro Tyr Met Thr Arg Glu Glu Arg Gly His Ala Ala 40 Leu Arg Arg Arg Glu Ala Phe Glu Ala Ile Lys Ala Ala Ala Thr Ser 55 60 Lys Phe Pro Pro His Arg Phe Ile Ala Asp Gln Leu Asp His Leu Asn 75 Xaa His Gln Glu Met Val Leu Ile Leu Ser Arg His Pro Trp Ile Leu 90 Trp Ile Thr Glu Leu Thr Ile Phe Thr Trp Ser Gly Leu Lys Asn Cys 105 Ser Leu Cys Glu Asn Glu Leu Trp Thr Ser Leu Tyr 120

<210> 505 <211> 59 <212> PRT <213> Homo sapiens

<220>

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<221> SIGNAL
<222> -14..-1
<400> 505
Met Ala Ala Leu Val Thr Val Leu Phe Thr Gly Val Arg Arg Leu His
                                  -5
              -10
Cys Ser Ala Xaa Leu Gly Arg Ala Ala Ser Gly Xaa Tyr Ser Arg Asn
                                          15
       5
                          10
Trp Leu Pro Thr Pro Pro Ala Thr Gly Pro Leu Pro Ser Ser Gln Thr
 20 25
Gly His Met Arg Met Ala Ala Leu Leu Pro Gln
                  40
<210> 506
<211> 101 .
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -36..-1
<400> 506
Met Gly Pro Tyr Asn Val Ala Val Pro Ser Asp Val Ser His Ala Arg
                                         -25
   -35
                      -30
Phe Tyr Phe Leu Phe His Arg Pro Leu Arg Leu Leu Asn Leu Leu Ile
                                    -10 .
                  -15
Leu Ile Glu Gly Ser Val Val Phe Tyr Gln Leu Tyr Ser Leu Leu Arg
                                             10
              1
Ser Glu Lys Trp Asn His Thr Leu Ser Met Ala Leu Ile Leu Phe Cys
                       20
Asn Tyr Tyr Val Leu Phe Lys Leu Leu Arg Asp Arg Xaa Xaa Leu Gly
                              40
              35
Arg Ala Tyr Ser Tyr Pro Leu Asn Ser Tyr Glu Leu Lys Ala Asn Xaa
Ala Ala Ser Xaa Gln
               65
<210> 507
<211> 341
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -55..-1
<400> 507
Met Arg Lys Val Val Leu Ile Thr Gly Ala Ser Ser Gly Ile Gly Leu
                   -50
                                     -45
Ala Leu Cys Lys Arg Leu Leu Ala Glu Asp Asp Glu Leu His Leu Cys
                                  -30
               -35
Leu Ala Cys Arg Asn Met Ser Lys Ala Glu Ala Val Cys Ala Ala Leu
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-15

20

Leu Ala Ser His Pro Thr Ala Glu Val Thr Ile Val Gln Val Asp Val
-5
1
5
Ser Asm Leu Gln Ser Phe Phe Arg Ala Ser Lys Glu Leu Lys Gln Arg

-20

15

-10

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Phe Gln Arg Leu Asp Cys Ile Tyr Leu Asn Ala Gly Ile Met Pro Asn
                                  35
Pro Gln Leu Asn Ile Lys Ala Leu Phe Phe Gly Leu Phe Ser Arg Lys
                              50
Val Ile His Met Phe Ser Thr Ala Glu Gly Leu Leu Thr Gln Gly Asp
                          65
Lys Ile Thr Ala Asp Gly Leu Gln Glu Val Phe Glu Thr Asn Val Phe
                                       · 85
Gly His Phe Ile Leu Ile Arg Glu Leu Glu Pro Leu Cys His Ser
                                      100
Asp Asn Pro Ser Gln Leu Ile Trp Thr Ser Ser Arg Ser Ala Arg Lys
               110
                                  115
                                                     120
Ser Asn Phe Ser Leu Glu Asp Phe Gln His Ser Lys Gly Lys Glu Pro
                              130
           125
Tyr Ser Ser Ser Lys Tyr Ala Thr Asp Leu Leu Ser Val Ala Leu Asn
                                             150
                          145
Arg Asn Phe Asn Gln Gln Gly Leu Tyr Ser Asn Val Ala Cys Pro Gly
                      160
                                         165
Thr Ala Leu Thr Asn Leu Thr Tyr Gly Ile Leu Pro Pro Phe Ile Trp
                  175
                                     180
Thr Leu Leu Met Pro Ala Ile Leu Leu Leu Arg Phe Phe Ala Asn Ala
              190
                                  195
Phe Thr Leu Thr Pro Tyr Asn Gly Thr Glu Ala Leu Val Trp Leu Phe
                                                 215
          205
                             210
His Gln Lys Pro Glu Ser Leu Asn Pro Leu Ile Lys Tyr Leu Ser Ala
                          225
                                              230
      220
Thr Thr Gly Phe Gly Arg Asn Tyr Ile Met Thr Gln Lys Met Asp Leu
                      240
                                         245
Asp Glu Asp Thr Ala Glu Lys Phe Tyr Gln Lys Leu Leu Glu Leu Glu
                   255
                                     260
Lys His Ile Arg Val Thr Ile Gln Lys Thr Asp Asn Gln Ala Arg Leu
                       275
               270
Ser Gly Ser Cys Leu
           285
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<210> 508 <211> 108 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -42..-1 <400> 508

Met His Ile Leu Gln Leu Leu Thr Thr Val Asp Asp Gly Ile Gln Ala -35 -30 Ile Val His Cys Pro Asp Thr Gly Lys Asp Ile Trp Asn Leu Leu Phe -20 -15 Asp Leu Val Cys His Glu Phe Cys Gln Ser Asp Asp Pro Ala Ile Ile -10 - 5 1 Leu Gln Xaa Gln Lys Thr Val Leu Ala Ser Val Phe Ser Val Leu Ser 1.5 10 Ala Ile Tyr Ala Ser Gln Thr Glu Gln Xaa Tyr Leu Lys Ile Xaa Lys 30 Gly Asp Gly Gly Ser Gly Ser Lys Gly Arg Pro Xaa Xaa Gln Thr Glu 45 50 Xaa Phe Leu Cys Ile Ser Lys Pro Ser Ser Phe Leu 60

<210> 509 <211> 80 <212> PRT

<210> 511 <211> 130 <212> PRT

<213> Homo sapiens

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<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 509
Met Glu Glu Ile Ser Ser Pro Leu Val Glu Phe Val Lys Val Leu Cys
               -20
                                -15
Thr Asn Gln Val Leu Ile Thr Ala Arg Ala Val Pro Thr Lys Lys Ala
                  - 5
                                   1
Ser Val Arg Cys Val Glu Lys Arg Phe Trp Ile Pro Lys Thr Thr Ser
                              15
          10
Lys His Leu Ser Arg Cys Ile Asp Gly Ile Ser Gly Phe Leu Asn Asp
                          30
Phe Thr Phe Cys Leu Glu Phe Ser Arg His Arg Cys Gln Leu Thr Glu
                                         50
<210> 510
<211> 158
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -44..-1
<400> 510
Met Ala Gly Phe Leu Asp Asn Phe Arg Trp Pro Glu Cys Glu Cys Ile
              -40
                                 -35
Asp Trp Ser Glu Arg Arg Asn Ala Val Ala Ser Val Val Ala Gly Ile
                              -20
                                                 -15
Leu Phe Phe Thr Gly Trp Trp Ile Met Ile Asp Ala Ala Val Val Tyr
                       -5
    -10
Pro Lys Pro Glu Gln Leu Asn His Ala Phe His Thr Cys Gly Val Phe
                10
                                     15
Ser Thr Leu Ala Phe Phe Met Ile Asn Ala Val Ser Asn Ala Gln Val
                                  30
              25
Arg Gly Asp Ser Tyr Glu Ser Gly Cys Leu Gly Arg Thr Gly Ala Arg
                               45
Val Trp Leu Phe Ile Gly Phe Met Leu Met Phe Gly Ser Leu Ile Ala
                          60
Ser Met Trp Ile Leu Phe Gly Ala Tyr Val Thr Gln Asn Thr Asp Val
                       75
                                          80
Tyr Pro Gly Leu Ala Val Phe Phe Gln Asn Ala Leu Ile Phe Phe Ser
                  90
                                     95
Thr Leu Ile Tyr Lys Phe Gly Arg Thr Glu Glu Leu Trp Thr
               105
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<220>
<221> SIGNAL
<222> -28..-1
<400> 511
Met Asn Trp Glu Leu Leu Leu Trp Leu Leu Val Leu Cys Ala Leu Leu
                               -20
                                                  -15
Leu Leu Leu Val Gln Leu Leu Arg Phe Leu Arg Ala Asp Gly Asp Leu
    -10
                           -5
Thr Leu Leu Trp Ala Glu Trp Gln Gly Arg Arg Pro Glu Trp Glu Leu
                   10
                                     15
Thr Asp Met Val Val Trp Val Thr Gly Ala Ser Ser Gly Ile Gly Glu
              25
                                  30
Glu Leu Ala Tyr Gln Leu Ser Lys Leu Gly Val Ser Leu Val Leu Ser
                              45
Ala Arg Arg Val His Glu Leu Glu Arg Val Lys Arg Arg Cys Leu Glu
                           60
Asn Gly Asn Leu Lys Glu Lys Asp Ile Leu Val Leu Pro Leu Asp Leu
                      75
                                         80
Thr Asp Thr Gly Ser His Glu Ser Gly Tyr Gln Ser Cys Ser Pro Gly
                  90
                                      95
Ile Trp
<210> 512
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<210> 512 <211> 199 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -62..-1

<400> 512 Met Ser Gln Arg Ser Leu Cys Met Asp Thr Ser Leu Asp Val Tyr Arg

-55 -50 Xaa Leu Ile Glu Leu Asn Tyr Leu Gly Thr Val Ser Leu Thr Lys Cys -40 -35 Val Leu Pro His Met Ile Glu Arg Lys Gln Gly Lys Ile Val Thr Val -25 -20 Asn Ser Ile Leu Gly Ile Ile Ser Val Pro Leu Ser Ile Gly Tyr Cys - 5 -10 Ala Ser Lys His Ala Leu Arg Gly Phe Phe Asn Gly Leu Arg Thr Glu 10 Leu Ala Thr Tyr Pro Gly Ile Ile Val Ser Asn Ile Cys Pro Gly Pro 25 Val Gln Ser Asn Ile Val Glu Asn Ser Leu Ala Gly Glu Val Thr Lys 40 45 Thr Ile Gly Asn Asn Gly Asn Gln Ser His Lys Met Thr Thr Ser Arg 60 Cys Val Arg Leu Met Leu Ile Ser Met Ala Asn Asp Leu Lys Glu Val 75 Trp Ile Ser Glu Gln Pro Phe Leu Leu Val Thr Tyr Leu Trp Gln Tyr 90 Met Pro Thr Trp Ala Trp Trp Ile Thr Asn Lys Met Gly Lys Lys Arg 110 105 Ile Glu Asn Phe Lys Ser Gly Val Asp Ala Xaa Ser Ser Tyr Phe Lys 120 125 Ile Phe Lys Thr Lys His Asp

135

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<211> 180
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -25..-1
<400> 513
Met Asn Thr Val Leu Ser Arg Ala Asn Ser Leu Phe Ala Phe Ser Leu
                   -20
                                      -15
Ser Val Met Ala Ala Leu Thr Phe Gly Cys Phe Ile Xaa Thr Ala Phe
        、 -5
                                   1
Lys Asp Arg Ser Val Pro Val Arg Leu His Val Ser Arg Ile Met Leu
                          15
Lys Asn Val Glu Asp Phe Thr Gly Pro Arg Glu Arg Ser Asp Leu Gly
                       30
Phe Ile Thr Phe Asp Ile Thr Ala Asp Leu Glu Asn Ile Phe Asp Trp
Asn Val Lys Gln Leu Phe Leu Tyr Leu Ser Ala Glu Tyr Ser Thr Lys
               60
                                   65
Asn Asn Ala Leu Asn Gln Xaa Val Leu Trp Asp Lys Ile Val Leu Arg
                               80
Gly Asp Asn Pro Lys Leu Leu Leu Lys Asp Met Lys Thr Lys Tyr Phe
                          95
Phe Phe Asp Asp Gly Asn Gly Leu Xaa Gly Asn Arg Asn Val Thr Leu
                      110
Thr Leu Ser Trp Asn Val Val Pro Asn Ala Gly Ile Leu Pro Leu Val
                  125
                                   130
Thr Gly Ser Gly His Val Ser Val Pro Phe Pro Asp Thr Tyr Glu Ile
                                 145
Thr Lys Ser Tyr
           155
<210> 514
<211> 120
<212> PRT
<213> Bos taurus
Met Met Thr Gly Arg Gln Gly Arg Ala Thr Phe Gln Phe Leu Pro Asp
                                  10
Glu Ala Arg Ser Leu Pro Pro Pro Lys Leu Thr Asp Pro Arg Leu Ala
                              25
Phe Val Gly Phe Leu Gly Tyr Cys Ser Gly Leu Ile Asp Asn Ala Ile
                           40
Arg Arg Pro Val Leu Leu Ala Gly Leu His Arg Gln Leu Leu Tyr
                       55
Ile Thr Ser Phe Val Phe Val Gly Tyr Tyr Leu Leu Lys Arg Gln Asp
                   70
                                       75
Tyr Met Tyr Ala Val Arg Asp His Asp Met Phe Ser Tyr Ile Lys Ser
                                   90
His Pro Glu Asp Phe Pro Glu Lys Asp Lys Lys Thr Tyr Gly Glu Val
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                              105
Phe Glu Glu Phe His Pro Val Arg
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115

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<211> 1082
<212> DNA
<213> Homo sapiens
<400> 515
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                                                                  120
taacaggate teetettgea gtetgeagee caggacgetg attecageag egeettaceg
cqcaqcccga agattcacta tggtgaaaat cgccttcaat acccctaccg ccgtgcaaaa
                                                                  180
                                                                  240
ggaggaggcg cggcaagacg tggaggccct cctgagccgc acggtcagaa ctcagatact
gaccggcaag gagctccgag ttgccaccca ggaaaaagag ggctcctctg ggagatgtat
                                                                  300
qcttactctc ttaggccttt cattcatctt ggcaggactt attgttggtg gagcctgcat
                                                                  360
                                                                  420
ttacaaqtac ttcatqcca aqaqcaccat ttaccqtgga gagatgtgct tttttgattc
                                                                  480
tqaqqatcct qcaaattccc ttcgtggagg agagcctaac ttcctgcctg tgactgagga
ggctgacatt cgtgaggatg acaacattgc aatcattgat gtgcctgtcc ccagtttctc
                                                                  540
                                                                  600
tgatagtgac cctgcagcaa ttattcatga ctttgaaaag ggaatgactg cttacctgga
                                                                  660
cttgttgctg gggaactgct atctgatgcc cctcaatact tctattgtta tgcctccaaa
aaatctggta gagctctttg gcaaactggc gagtggcaga tatctgcctc aaacttatgt
                                                                  720
ggttcgagaa gacctagttg ctgtggagga aattcgtgat gttagtaacc ttggcatctt
                                                                  780
                                                                  840
tatttaccaa ctttgcaata acagaaagtc cttccgcctt cgtcgcagag acctcttgct
gggtttcaac aaacgtgcca ttgataaatg ctggaagatt agacacttcc ccaacgaatt
                                                                  900
                                                                  960
tattgttgag accaagatct gtcaagagta agaggcaaca gatagagtgt ccttggtaat
aaqaaqtcaq aqatttacaa tatqacttta acattaaqqt ttatgggata ctcaagatat
                                                                 1020
                                                                 1080
1082
<210> 516
<211> 559
<212> DNA
<213> Homo sapiens
<400> 516
ctgctccagc gctgacgccg agccatggcg gacgaggagc ttgaggcgct gaggagacag
                                                                   60
                                                                  120
aggetggeeg agetgeagge caaacaeggg gateetggtg atgeggeeca acaggaagea
aagcacaggg aagcagaaat gagaaacagt atcttagccc aagttctgga tcagtcggcc
                                                                  180
cgggccaggt taagtaactt agcacttgta aagcctgaaa aaactaaagc agtagagaat
                                                                  240
                                                                  300
taccttatac agatggcaag atatggacaa ctaagtgaga aggtatcaga acaaggttta
atagaaatcc ttaaaaaagt aagccaacaa acagaaaaga caacaacagt gaaattcaac
                                                                  360
                                                                  420
agaagaaaag taatggactc tgatgaagat gacgattatt gaactacaag tgctcacaga
ctagaactta acggaacaag tctaggacag aagttaagat ctgattattt actttgttta
                                                                  480
                                                                  540
559
aaaaaaaaa aaaaaaaaa
<210> 517
<211> 110
<212> PRT
<213> Homo sapiens
<400> 517
Met Phe Cys Pro Leu Lys Leu Ile Leu Leu Pro Val Leu Leu Asp Tyr
                                  10
                                                     15
Ser Leu Gly Leu Asn Asp Leu Asn Val Ser Pro Pro Glu Leu Thr Val
                              25
           20
His Val Gly Asp Ser Ala Leu Met Gly Cys Val Phe Gln Ser Thr Glu
                                             4.5
                           40
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Asp Lys Cys Ile Phe Lys Ile Asp Trp Thr Leu Ser Pro Gly Glu His
                       55
Ala Lys Asp Glu Tyr Val Leu Tyr Tyr Tyr Ser Asn Leu Ser Val Pro
                   70
65
                                       75
Ile Gly Arg Phe Gln Asn Arg Val His Leu Met Gly Asp Asn Leu Cys
               85
                                   90
Asn Asp Gly Ser Leu Leu Gln Asp Val Gln Asp Val Glu
           100
                                105
                                                    110
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<400> 518

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<213> Mus musculus

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January 31, 2005

Global IP Estimate - Summary Application Information Type: PCT Patent - National Phase PRI-002PCT

Pages in Application (excluding Drawings)	39
Pages of Claims	3
Pages of Drawings	3
Pages for Translation excluding Claims	36
Pages for Translation	36
Number of Claims	10
Number of Claims for Japan	10
Number of Convention Priorities	3
Number of Designations for EPO	7
Number of Extensions for EPO	0
PCT Chapter II filed	Yes
Applicant is Assignee	No
Late Filing of Power of Attorney	No
PCT filing date after July 1, 1999	Yes
Filer is a Large Entity	Yes
Application Sent by Facsimile	Yes
Courier Used	Yes
JP applic filed after April 1, 2004	Yes
JP exam request after April 1, 2004	Yes
Priority Month/Year: 8/2002	

Application Month/Year: 2/2005 Report Start Month/Year: 1/2005 Report End Month/Year: 1/2025

AU Australia

	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	<u>Miscell.</u>	<u>In-House</u>	<u>Total</u>
Filing	\$247	\$1,669	\$0	\$164	\$800	\$2,880
Examination	\$263	\$410	\$0	\$0	\$300	\$973
Granting	\$108	\$387	\$0	\$0	\$250	\$745
Total	\$618	\$2,466	\$0	\$164	\$1,350	\$4,598
Total Annuities: \$10,510				Total I	ncluding Annuiti	es: \$15,108

Exchange rate: 1.2931 Australian Dollars/US \$; Annuities calculated from filing date

CA Canada

	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	Miscell.	<u>In-House</u>	<u>Total</u>
Filing	\$323	\$694	\$0	\$164	\$800	\$1,981
Examination	\$645	\$262	\$0	\$0	\$300	\$1,207
Granting	\$242	\$303	\$0	\$0	\$250	\$795
Total	\$1,210	\$1,259	\$0	\$164	\$1,350	\$3,983
Total Appuities: \$8.856				Total I	actudina Appuiti	ac: \$12 830

Exchange rate: 1.2394 Canadian Dollars/US \$; Annuities calculated from filing date

EP European Patent Office

	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	Miscell.	<u>In-House</u>	<u>Total</u>
Filing	\$1,746	\$2,249	\$0	\$164	\$1,450	\$5,609
Examination	\$1,864	\$651	\$0	\$0	\$300	\$2,815
Granting	\$1,023	\$896	\$492	\$0	\$250	\$2,661
Total	\$4,633	\$3,796	\$492	\$164	\$2,000	\$11,085
Total Annuities: \$4,292				Total li	ncluding Annuit	ies: \$15,377

Exchange rate: 0.5299 British Pounds/US \$; 0.7673 Euros/US \$; 0.7673 Euros/US \$; Annuities calculated from filing date

JP Japan

	<u>Official</u>	Associate	<u>Translation</u>	Miscell.	In-House	<u>Total</u>
Filing	\$155	\$2,072	\$5,043	\$164	\$800	\$8,234
Examination	\$1,813	\$522	\$0	\$0	\$300	\$2,635
Granting	\$133	\$300	\$0	\$0	\$250	\$683
Total	\$2,101	\$2,894	\$5,043	\$164	\$1,350	\$11,552
Total Annuities: \$10 988				Total I	ncludina Annuiti	es: \$22 540

Exchange rate: 103.51 Japanese Yen/US \$; Annuities calculated from grant date

EPO - Validation Phase

AL Albania

	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	<u>Miscell.</u>	<u>In-House</u>	<u>Total</u>
Filing	\$79	\$782	\$162	\$0	\$375	\$1,398
Total	\$79	\$782	\$162	\$0	\$375	\$1,398
Total Annuities: \$8,080				Total	Including Annui	ties: \$9,478

Exchange rate: 101.71 Albanian Leke/US \$; 0.5299 British Pounds/US \$; 20% VAT added to Associate's charges and Translation costs; Annuities calculated from filing date

AT Austria

	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	<u>Miscell.</u>	<u>In-House</u>	<u>Total</u>
Filing	\$1,338	\$1,237	\$2,815	\$0	\$375	\$5,765
Total	\$1,338	\$1,237	\$2,815	\$0	\$375	\$5,765
Total Annuities: \$16,861				Total Ir	ncluding Annuiti	es: \$22,626

Exchange rate: 0.7673 Euros/US \$; 0.5299 British Pounds/US \$; Annuities calculated from publication date

BE Belgium

	Official Official	<u>Associate</u>	<u>Translation</u>	Miscell.	In-House	<u>Total</u>
Filing	\$0	\$885	\$2,627	\$0	\$375	\$3,887
Total	\$0	\$885	\$2,627	\$0	\$375	\$3,887
Total Annuities: \$8 786				Total I	ncludina Annuiti	es: \$12.673

Exchange rate: 0.7673 Euros/US \$; 0.5299 British Pounds/US \$; Annuities calculated from filing date

BG Bulgaria

_	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	Miscell.	<u>In-House</u>	<u>Total</u>
Filing	\$53	\$707	\$325	\$0	\$375	\$1,460
Total	\$53	\$707	\$325	\$0	\$375	\$1,460
Total Annuities: \$12.858				Total I	ncludina Annuiti	es: \$14.318

Exchange rate: 0.5299 British Pounds/US \$; 1.5079 Bulgarian Lev/US \$; Annuities calculated from filing date

CH Switzerland

	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	Miscell.	In-House	<u>Total</u>
Filing	\$0	\$950	\$4,092	\$0	\$375	\$5,417
Total	\$0	\$950	\$4,092	\$0	\$375	\$5,417
Total Annuities: \$8,840				Total Ir	ncluding Annuiti	es: \$14,257

Exchange rate: 1.1877 Swiss Francs/US \$; 0.5299 British Pounds/US \$; Annuities calculated from filing date

CY Cyprus

	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	Miscell.	<u>In-House</u>	<u>Total</u>
Filing	\$111	\$881	\$1,863	\$0	\$375	\$3,230
Total	\$111	\$881	\$1,863	\$0	\$375	\$3,230
Total Annuities: \$6,711		•		Total	Including Annui	ties: \$9,941

Exchange rate: 0.4497 Cypriot Pounds/US \$; 0.5299 British Pounds/US \$; 15% VAT added to Associate's charges and Translation costs

CZ Czech Republic

	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	<u>Miscell.</u>	<u>In-House</u>	<u>Total</u>
Filing	\$52	\$697	\$1,656	\$0	\$375	\$2,780
Total	\$52	\$697	\$1,656	\$0	\$375	\$2,780
Total Annuities: \$10 747				Total Ir	ncludina Annuiti	es: \$13 527

Exchange rate: 23.22 Czech Korunas/US \$; 0.5299 British Pounds/US \$; Annuities calculated from filing date

DE	Ger	rma	nv
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	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	<u>Miscell.</u>	<u>In-House</u>	<u>Total</u>
Filing	\$195	\$963	\$3,284	\$0	\$375	\$4,817
Total	\$195	\$963	\$3,284	\$0	\$375	\$4,817
Total Appuities: \$22,293				Total In	scludina Annuiti	es: \$27 110

Exchange rate: 0.7673 Euros/US \$; 0.5299 British Pounds/US \$; Annuities calculated from filing date

DK Denmark

	<u>Official</u>	<u>Associate</u>	<u>I ranslation</u>	<u>Miscell.</u>	<u>In-House</u>	<u>l otal</u>
Filing	\$282	\$1,063	\$4,255	\$0	\$375	\$5,975
Total	\$282	\$1,063	\$4,255	\$0	\$375	\$5,975
Total Annuities: \$12,116				Total Ir	ncluding Annuiti	es: \$18,091

Exchange rate: 0.5299 British Pounds/US \$; 5.7107 Danish Krone/US \$; Annuities calculated from filing date

EE Estonia

	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	<u>Miscell.</u>	<u>In-House</u>	<u>Total</u>
Filing	\$58	\$670	\$2,674	\$0	\$375	\$3,777
Total	\$58	\$670	\$2,674	\$0	\$375	\$3,777
Total Annuities: \$10,368				Total Ir	ncluding Annuiti	es: \$14,145

Exchange rate: 12.00798 Kroon/US \$; 0.5299 British Pounds/US \$; 0.7673 Euros/US \$; Annuities calculated from filing date

ES Spain

	Official	<u>Associate</u>	<u>I ranslation</u>	Miscell.	<u>In-House</u>	<u>I otal</u>
Filing	\$588	\$1,029	\$2,815	\$0	\$375	\$4,807
Total	\$588	\$1,029	\$2,815	\$0	\$375	\$4,807
Total Annuities: \$11,696				Total Ir	ncludina Annuiti	es: \$16.503

Exchange rate: 0.5299 British Pounds/US \$; 0.7673 Euros/US \$; Annuities calculated from filing date

FI Finland

	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	Miscell.	<u>In-House</u>	<u>Total</u>
Filing	\$606	\$1,990	\$3,753	\$0	\$375	\$6,724
Total	\$606	\$1,990	\$3,753	\$0	\$375	\$6,724
Total Annuities: \$12 799				Total Ir	actudina Annuiti	es: \$19.523

Exchange rate: 0.7673 Euros/US \$; 0.5299 British Pounds/US \$; Annuities calculated from filing date

FR France

	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	Miscell.	<u>In-House</u>	<u>Total</u>
Filing	\$46	\$977	\$3,050	\$0	\$375	\$4,448
Total	\$46	\$977	\$3,050	\$0	\$375	\$4,448
Total Annuities: \$10.395				Total Ir	ncludina Annuiti	es: \$14.843

 $\textbf{Exchange rate: 0.7673 Euros/US \$; 0.5299 \ British \ Pounds/US \$; Annuities \ calculated \ from \ filing \ date }$

GB United Kingdom

	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	Miscell.	<u>In-House</u>	<u>Total</u>
Filing	\$0	\$658	\$0	\$0	\$375	\$1,033
Total	\$0	\$658	\$0	\$0	\$375	\$1,033
Total Annuities: \$10,065				Total Ir	ncluding Annuiti	ies: \$11,098

Exchange rate: 0.5299 British Pounds/US \$; Annuities calculated from filing date

GR Greece

	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	Miscell.	<u>In-House</u>	<u>Total</u>
Filing	\$390	\$1,015	\$1,512	\$0	\$375	\$3,292
Total	\$390	\$1,015	\$1,512	\$0	\$375	\$3,292
Total Annuities: \$9,944				Total I	ncludina Annuiti	es: \$13 236

Exchange rate: 0.7673 Euros/US \$; 0.5299 British Pounds/US \$; Annuities calculated from filing date

HR Croatia

	<u>Official</u>	Associate	Translation	Miscell.	In-House	Total
Filing	\$ 0	\$1,248	\$1,836	\$0	\$375	\$3,459
Total	\$0	\$1,248	\$1,836	_\$0 	\$375	\$3,459
Total Annuities: \$7,724				lotali	ncluding Annuit	ies: \$11,183
Exchange rate: 0.5299 British Pound	s/US \$; 0.7673 Euro	s/US \$; 5.9001 Cr	oatian Kuna/US \$			
HU Hungary						
ET.	Official 6700	Associate	<u>Translation</u>	Miscell.	In-House	<u>Total</u>
Filing Total	\$733 \$733	\$1,216 \$1,216	\$3,050 \$3,050	\$0 \$0	\$375 \$375	\$5,374 \$5,374
Total Annuities: \$15,474	Φ133	\$1,210	\$3,030	•	ສວາວ ncluding Annuit	
Exchange rate: 0.5299 British Pound	s/US \$; 0.7673 Euro	s/US \$; 188.23 Hu	ungarian Forints/US \$			
IE Ireland						
ic netalio	Official	Associate	Translation	Miscell.	In-House	Total
Filing	\$46	\$990	\$0	\$0	\$375	\$1,411
Total	\$46	\$990	\$0	\$0	\$375	\$1,411
Total Annuities: \$10,036	4.0	4000	40	* -	ncluding Annuit	
Exchange rate: 0.7673 Euros/US \$; ().5299 British Pound	s/US \$; Annuities	calculated from filing	date		
IT Italy						
	Official	Associate	Translation	Miscell.	In-House	Total
Filing	\$57	\$898	\$2,520	<u>\$0</u>	\$375	\$3,850
Total	\$57	\$898	\$2,520	\$0	\$375	\$3,850
Total Annuities: \$12,716	•		, ,	Total I	ncluding Annuit	
Exchange rate: 0.7673 Euros/US \$; (0.5299 British Pound	s/US \$; Annuities	calculated from filing	date		
LT Lithuania						
Li Liuidailla	Official	Associate	Translation	Miscell.	In-House	Total
Filing	\$60	\$652	\$108	\$0	\$375	\$1,195
Total	\$60	\$652	\$108	\$0	\$375	\$1,195
Total Annuities: \$5,998	***	V	****	* -	Including Annu	
Exchange rate: 2.649275 Litas/US \$;	0 5200 British Pour	de/IIS \$				
-	0.5233 Billian i Oui	103/00 ¥				
LU Luxembourg						-
-	Official 210	<u>Associate</u>	Translation	Miscell.	In-House	<u>Total</u>
Filing	\$18	\$533	\$0 \$0	\$0 \$0	\$375	\$926
Total Appuition \$6,624	\$18	\$533	\$0	\$0	\$375	\$926
Total Annuities: \$6,624				TOtal	Including Annu	illes. \$7,550
Exchange rate: 0.7673 Euros/US \$; (0.5299 British Pound	s/US \$; Annuities	calculated from filing	date		
LV Latvia	055-:-1	A : - 4 -	Topoglotica	A4 :II	la Havaa	Tatal
Filian	Official	Associate	<u>Translation</u>	Miscell.	In-House	Total
Filing Total	\$47 \$47	\$452 \$452	\$177 \$177	\$0 \$0	\$375 \$375	\$1,051 \$1,051
Total Annuities: \$7,503	Φ4 1	\$452	\$177	· ·	Including Annu	
Exchange rate: 0.5299 British Pound	s/US \$; 0.534 Lats/U	JS \$; 0.7673 Euros	s/US \$		J	
-						
MC Monaco	<u>Official</u>	<u>Associate</u>	Translation	Miscell.	In-House	Total
Filing	\$54	\$735	\$0	\$0	\$375	\$1,164
Total	\$54	\$735	\$0	\$0	\$375	\$1,164
Total Annuities: \$7,246	ΨΟ¬	Ψ,00	Ψ0	•	Including Annu	
Exchange rate: 0.5299 British Pound	s/US \$; 0.7673 Euro	s/US \$; Annuities	calculated from filing	date		
MK Macedonia						
	Official	<u>Associate</u>	<u>Translation</u>	Miscell.	In-House	<u>Total</u>
Filing	\$27	\$627	\$120	\$0	\$375	\$1,149

Total \$27 \$627 \$120 \$0 \$375 \$1,149
Total Annuities: \$4,615 Total Including Annuities: \$5,764

Exchange rate: 0.5299 British Pounds/US \$; 56.6137 Denars/US \$

NL Netherlands

	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	Miscell.	<u>In-House</u>	<u>Total</u>
Filing	\$33	\$631	\$3,941	\$0	\$375	\$4,980
Total	\$33	\$631	\$3,941	\$0	\$375	\$4,980
Total Annuities: \$12 500				Total Ir	cludina Annuiti	es: \$17 480

Exchange rate: 0.7673 Euros/US \$; 0.5299 British Pounds/US \$; Annuities calculated from filing date

PL Poland

	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	Miscell.	<u>In-House</u>	<u>Total</u>
Filing	\$88	\$507	\$2,520	\$0	\$375	\$3,490
Total	\$88	\$507	\$2,520	\$0	\$375	\$3,490
Total Annuities: \$7 323				Total Ir	ncludina Annuiti	es: \$10.813

Exchange rate: 3.1128 Polish Zloty/US \$; 0.5299 British Pounds/US \$; 0.7673 Euros/US \$; Annuities calculated from grant date

PT Portugal

	<u>Official</u>	<u>Associate</u>	Iranslation	Miscell.	<u>In-House</u>	<u>Total</u>
Filing	\$149	\$1,352	\$2,520	\$0	\$375	\$4,396
Total	\$149	\$1,352	\$2,520	\$0	\$375	\$4,396
Total Annuities: \$10.587				Total In	ncludina Annuiti	es: \$14.983

Exchange rate: 0.7673 Euros/US \$; 0.5299 British Pounds/US \$; Annuities calculated from filing date

RO Romania

	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	<u>Miscell.</u>	<u>In-House</u>	<u>Total</u>
Filing	\$220	\$993	\$1,152	\$0	\$375	\$2,740
Total	\$220	\$993	\$1,152	\$0	\$375	\$2,740
Total Annuities: \$10,237				Total Ir	ncludina Annuiti	es: \$12.977

Exchange rate: 0.5299 British Pounds/US \$; 0.7673 Euros/US \$; Annuities calculated from filing date; Annuities accumulated until Grant

SE Sweden

	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	<u>Miscell.</u>	<u>In-House</u>	<u>Total</u>
Filing	\$912	\$1,514	\$4,328	\$0	\$375	\$7,129
Total	\$912	\$1,514	\$4,328	\$0	\$375	\$7,129
Total Annuities: \$6,046				Total li	ncludina Annuiti	es: \$13 175

Exchange rate: 6.9863 Swedish Krona/US \$; 0.5299 British Pounds/US \$; Annuities calculated from grant date

SI Slovenia

	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	<u>Miscell.</u>	<u>In-House</u>	<u>Total</u>
Filing	\$16	\$717	\$180	\$0	\$375	\$1,288
Total	\$16	\$717	\$180	\$0	\$375	\$1,288
Total Annuities: \$4,930				Total	Including Annui	ties: \$6,218

Exchange rate: 0.5299 British Pounds/US \$; 186.18 Tolars/US \$; 0.7673 Euros/US \$

SK Slovakia

	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	Miscell.	In-House	<u>Total</u>
Filing	\$0	\$697	\$1,512	\$0	\$375	\$2,584
Total	\$0	\$697	\$1,512	\$0	\$375	\$2,584
Total Annuities: \$4,506				Total	Including Annui	ties: \$7 090

Exchange rate: 0.5299 British Pounds/US \$; 29.417 Slovak Koruna/US \$

TR Turkey

	<u>Official</u>	<u>Associate</u>	<u>Translation</u>	<u>Miscell.</u>	<u>In-House</u>	<u>Total</u>
Filing	\$432	\$799	\$1,912	\$0	\$375	\$3,517
Total	\$432	\$799	\$1,912	\$0	\$375	\$3,517
Total Annuities: \$10,884				Total In	ncludina Annuiti	es: \$14 401

Exchange rate: 0.5299 British Pounds/US \$; 1.3478 Million Turkish Lira/US \$; 18% VAT added to Associate's charges and Translation costs; Annuities calculated from filing date

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